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IMPRESSIONS OF THE VALUE OF MEGAVOLTAGE IRRADIATION IN THE TREATMENT OF MALIGNANT NEOPLASIA.

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MEGAVOLTAGE IRRADIATION employs an ionizing beam—either of X rays or gamma rays—in the million-volt range. It has been employed in the treatment of cancer in the United Kingdom for the past decade; in Australia this method has been available only for the past three years.

In the medical literature there has been scant reference to the indications for this form of treatment, and what reports have appeared have been confined to the more special journals away from the reading of the average physician, surgeon or general practitioner. There have been no statements as to five-year cure rates, because insufficient numbers of patients have received megavoltage irradiation for the purpose of any statistical survey. The purpose in presenting this paper is to give a guide, however rough, to the indications for this more recent form of treatment and to give some pointer to the results to

be expected in certain groups of tumours. These impressions are based upon my experiences gained whilst working at the Hammersmith Hospital, the Royal Marsden Hospital and the Royal Adelaide Hospital.

Megavoltage radiotherapy is employed in Australia by means of the linear accelerators in Brisbane, Adelaide and Melbourne, and the radioactive cobalt units in Sydney and Launceston; a linear accelerator will be installed in Perth in the near future, whilst cobalt units are to be used soon in Adelaide. Linear accelerators emit X rays, whilst cobalt units give out gamma rays. For practical purposes these two forms of apparatus are not dissimilar in their clinical applications and effects. It is possible to rotate some of the cobalt beam units so that a high dosage can be given to a particular volume of tissue with relatively lower dosage being received by neighbouring normal parts in the path of the beam. In practice, however, I have found no great clinical advantage to be gained by the use of the rotating beam in preference to the stationary type.

The Advantages of Megavoltage Irradiation over Conventional X-Ray Therapy.

X rays generated by a voltage in the range of 200 to 400 K.V. (commonly called conventional X rays or "deep" X rays) have been used in all Australian capital cities

for radiotherapy over the past generation. The beam produced by these plants is absorbed very readily by tissue, especially by bone and cartilage. Therefore, an undesirably large proportion of the useful part of the beam does not reach a specified volume deep to the skin in adequate quantity. Thus, when dealing with a deep-seated tumour, it is necessary to deliver the irradiation through multiple skin "fields"—sometimes eight are required—and each field receives as much irradiation as it will tolerate, thus causing moist desquamation of the epithelium with its attendant discomforts and scarring.

In contradistinction, the megavoltage beam is absorbed less easily by tissue; again, for practical purposes, the fraction of the beam absorbed by bone and cartilage is almost equal to that absorbed by muscle, fat and connective tissue. Thus, to deliver a heavy dosage to a deep site, only two, three or four fields are required, since the megavoltage beam penetrates more effectively to the deeper structures.

At the point of entry of the megavoltage beam on the skin, there is only a minimal amount of irradiation absorbed, the resultant effect being that a visible skin reaction does not take place. The intensity of the beam builds up to a maximum after it has penetrated to about 1 cm. from the skin surface. However, when the path of the megavoltage beam crosses a mucous surface, a reaction is seen similar to that caused by conventional X rays. This complication, although troublesome, is dealt with by simple local treatment to the affected mucosa and does not constitute any serious problem in trained hands.

It is a common experience that radiation sickness is seen less frequently when megavoltage therapy is applied, whereas it is a troublesome and almost constant complication of conventional X-ray treatment.

An important advantage of the use of the megavoltage beam is demonstrated when one is irradiating through bone or cartilage. Since conventional X rays are relatively easily absorbed by bone or cartilage, a very heavy localized dose is produced upon included, or immediately adjacent, soft tissue elements. This can cause irradiation osteomyelitis or perichondritis, especially if infection is a superadded complication; also a very severe local reaction is seen on any adjacent mucous surface. The risk of these undesirable complications is not seen to such a marked extent when megavoltage irradiation is employed, because a relatively smaller proportion of the beam is absorbed by bone or cartilage than is the case with conventional X rays.

The technique of applying the megavoltage beam to the patient—the setting-up procedure—is a relatively simpler process than that necessary when the conventional units are used. In most cases only one to four skin fields are required in the former instance. The daily treatment time is much reduced because the megavoltage apparatus is of greater output than the older equipment; e.g. the linear accelerator at the Royal Adelaide Hospital can deal with about sixty patients per working day, whereas conventional equipment would give treatment to about twenty over the same working time.

The effects of the megavoltage beam in terms of response of the tumour to treatment is that, provided that the tumour is sensitive to this form of irradiation, palliative radiotherapy is more easily, more quickly and more effectively given than by conventional X-ray plants. Some radio-biologists are of the opinion that there is no enhancement of the biological effects of this beam when compared with conventional X rays. In point of fact, an improvement in response is often obtained: first, for equivalent dosage absorbed, accessible tumours treated by the megavoltage method respond to a more marked degree than that obtained when conventional X rays are used; secondly, some types of tumour respond to megavoltage irradiation when experience has shown that they are resistant to conventional X rays. Strickland (1958) has collected a series of 20 chordomata treated over the past three years, using a cobalt beam unit: all resolved after treatment and have remained quiescent. Further,

certain sarcomata have shown a pleasing initial result when irradiated by a megavoltage beam.

Impressions of the Effects of Megavoltage Irradiation upon Specific Groups of Tumours.

Megavoltage irradiation has not effected any significant improvement with respect to cure when used for treatment of the following: (i) malignant melanoma; (ii) gastro-intestinal carcinoma; (iii) lung carcinoma; (iv) tumours of lymphoid tissue (the reticulos—Hodgkin's disease, reticulum-cell sarcoma, lymphosarcoma and allied diseases); (v) most sarcomata; (vi) most brain tumours, except medulloblastoma and pituitary tumours; (vii) ovarian tumours; (viii) prostatic tumours; (ix) pancreatic tumours.

Tumours of the Head and Neck.

It is my opinion that any radio-sensitive carcinoma in the head and neck from the base of the skull to the clavicles should be treated by radiotherapy in the first instance. Surgery should be reserved to deal with residuum, recurrence or operable lymph nodes as a second line of attack. Radiotherapy is always more effective when dealing with tissue which has not been subjected to surgical trauma; also, a cure is possible with only moderate discomfort, minimal deformity and negligible mutilation. Provided surgery, if necessary, is performed within about six months after megavoltage irradiation, there should not be any gross problems to the operator with regard to irradiation-induced fibrosis and troublesome haemorrhage. Mill, writing in Raven's textbook, "Cancer", states: "Healing after teleradium (or telecobalt) is no more delayed than if no such treatment had been given. . . . Healing, if laryngectomy has to be undertaken, is more satisfactory after teleradium than after high-voltage (conventional) X-ray therapy." Both teleradium and telecobalt units mentioned by him emit a beam of gamma rays in the megavoltage range.

The following group of tumours has been shown to respond to megavoltage irradiation in a most encouraging manner: (i) skin carcinoma involving bone or cartilage; (ii) carcinoma of the posterior one-third of the tongue; (iii) carcinoma of the hard and soft palates, alveolus, floor of the mouth and buccal mucosa; (iv) carcinoma of the naso-pharynx and antro-ethmoid sinuses; (v) carcinoma of the middle ear; (vi) carcinoma of the vocal cord. However, bulky and very indurated tumours in this group have not responded in a satisfying fashion. This is probably due to the reduced oxygen tension in the deeper portions of the tumour, causing a local relative radio-resistance (Gray, 1957).

Advanced tumours of the vocal cord—especially those with subglottic extension—are responding in a disappointing fashion, although the results of treatment by the megavoltage method are superior to those of conventional X rays. However, in five years' experience with a cobalt unit, Smith (1957) found that five out of six subglottic tumours responded.

The results obtained by the group working at St. Thomas's Hospital, London, using radiotherapy under conditions of increased oxygenation, may lead to a more satisfactory outcome in some of these cases. Conventional X-ray therapy has a poor record in the treatment of almost all the tumours enumerated above, and there is no doubt that the megavoltage form has given better initial response than that obtained previously.

There is a second group in the head and neck which is not providing grounds for optimism when submitted to megavoltage irradiation. It comprises: (i) carcinoma of the tonsil—especially the linguo-tonillar sulcus; (ii) carcinoma of the aryepiglottic fold and pyriform fossa; (iii) supraglottic tumours and tumours of the infrayohoid epiglottis; (iv) carcinoma of the parotid; (v) carcinoma of the thyroid; (vi) carcinoma of the post-cricoid region; (vii) carcinoma of the oesophagus.

One can point to individual cases amongst those seen over the past five years which have shown an improved response over that usually obtained by conventional

methods. However, it would appear that the general trend in this latter group is that they are less sensitive than the former group to megavoltage irradiation. Again, one hopes for further work in the field of radio-sensitizers, chemotherapy or increased oxygen tension technique to deal more effectively with this group, because it is clear that results from surgery in this region will not improve the outcome for these patients.

Tumours of the Bladder.

Where the tumour is too large to implant with radon seeds (greater than 5 cm. in diameter) or extension has occurred into the perivesical tissues, or multiple superficial lesions are present, supervoltage irradiation has made a dramatic change in the outlook for these cases. If cures in a proportion of cases will not be realized in the future, then at least there is hope for a term of palliation much longer than that obtained by conventional X-ray methods. The degree of infiltration, the metastatic spread in the pelvis and the histological grading of the tumour are all factors of prognostic significance when the results to be expected are assessed. In terms of palliation, the haematuria stops, pain is relieved, there is gain in weight and increase in the patient's well-being in those cases which respond to treatment. A mucosal reaction is seen in the bladder, giving rise to frequency of micturition and dysuria, but this reaction is not as marked as that caused by conventional techniques. However, in those cases which show an initial response, cystoscopic examination shows shrinkage of the primary tumour, and infiltration is found to have been reduced on rectal examination. Most radiotherapists using megavoltage equipment agree that great strides have been made in the treatment of bladder carcinoma.

Minty (1958), using a linear accelerator in Melbourne, found that "fairly high doses were given with very little discomfort to the patients". His impression after treating 50 cases of bladder cancer during 1957 and 1958 was that the proportion surviving at present was greater than that to be expected from the use of conventional techniques.

Carcinoma of the Uterus.

Megavoltage irradiation seems to play no part in the curative treatment of adenocarcinoma of the body of the uterus. These tumours are resistant sometimes to even local application of radium, and therefore, although this latter technique is of great value in the treatment of these lesions, I have not found any improvement in the over-all results by using megavoltage equipment.

In contradistinction, it is felt that the megavoltage beam will play an important part in the treatment of carcinoma of the cervix. I have had most encouraging responses following a technique using the principles laid down by Lederman. In particular, the more advanced Stage II and Stage III lesions have responded in a manner which is a definite improvement upon the results obtained by the use of radium and conventional X-ray therapy. I have used the megavoltage beam in a judicious combination with intracavitary radioactive sources and have obtained satisfying shrinkage of the primary tumour and disappearance of palpable malignant infiltration. Moreover, in those cases which have proved to be sensitive to this form of treatment—and these form the larger proportion of patients referred for treatment—pieces taken for histological examination and smears examined by the Papanicolaou technique have shown no recurrent neoplasm. One would not have expected such an encouraging effect if conventional methods were employed. In a small series of carcinoma of the cervical stump, following upon subtotal hysterectomy performed many years previously, I have had a most pleasing response to this form of treatment.

Provided that this form of irradiation is given in close consultation with a gynaecologist, the radiotherapist, using simple principles which are part of the English school of radiotherapy, can expect very little in the way of undesirable side effects in terms of diarrhoea and radiation sickness. In no case in a personal series has there been

any radio-necrotic rectal or bladder ulceration due to the technique of treatment. Although gynaecologists averse to irradiation in the treatment of cervical carcinoma lay great stress upon what they term "burns", this complication in a properly conducted radiotherapy centre is of the order of 1 in 100 cases (Kottmeier, 1953).

Osteosarcoma of Bone.

In the treatment of osteosarcoma, surgery alone has not proved to be of any value. Cade is the champion of irradiation by the megavoltage method, and he advocates surgical treatment for those cases which (1) recur after radiotherapy, provided no metastases are found, or (2) if it is considered that the limb becomes a burden to the patient by reason of (a) contracture, (b) severe pain, or (c) ulceration. In his series reported in the British Empire Cancer Campaign report of 1957, the five-year survival figure for 18 cases is 27.7%. Conventional X-ray therapy has never given results comparable with these, and, bad as they are, they are at least an improvement on surgery, with the added advantage that the patients (and their parents) are often spared the mental stress of a mutilating amputation.

Conclusions.

1. It is believed that the megavoltage units, with the use of either X or gamma rays, have made a most valuable contribution towards improving the outlook for patients with certain types of tumour.

2. These types of tumours have been grouped according to one radiotherapist's impressions. In the passage of time it is almost certain that revision of these groups will be necessary.

3. Palliative treatment can be given with greater ease and with more speed by the use of megavoltage irradiation than was possible with conventional machines. These latter units are rendered obsolete by modern standards, and there is no good reason why they should be considered in any plans for future radiotherapy departments. Radiotherapists at the Christie Hospital, Manchester (British Empire Cancer Campaign Report, 1957: 285), have found that rotation therapy, using conventional X-ray equipment, has no great advantage over the fixed-beam apparatus; my own opinion confirms this view, and I have found that rotating conventional X-ray units are far inferior to the linear accelerator or the cobalt-beam unit.

4. Although the planning and the techniques of application of megavoltage irradiation are easier than older methods, the radiotherapist must exert a high degree of care for each individual patient. Ideally, the treatment should be planned as a team effort in close cooperation with the referring surgeon or physician; I believe it is almost vital for the patient to be seen whilst undergoing treatment by both parties concerned. Frequent examinations during the treatment period are most essential; for example, with respect to laryngeal growths, it is found sometimes that a daily inspection of the larynx may be necessary to watch progress and to guard against any respiratory obstruction.

Radiotherapy as a specialty is one of the more recent branches of medicine, and its development has progressed in a stormy fashion. It is not surprising that many medical men have a very prejudiced view towards it. The good work done by the competent radiotherapist is often forgotten, whereas his mistakes and the results of the incompetent worker are remembered. The confidence of other members of the medical profession must be captured by the radiotherapist, because it is by cooperation between them and himself that a better knowledge of clinical cancer will be gained. Too few surgeons have a working acquaintance with cancer as a general and particular problem, and many would benefit from the advice of a radiotherapist who deals with cancer every day.

Finally, this cooperative and consultative teamwork should be maintained throughout any further treatment, and particularly over the follow-up period. The mutual

benefit to all parties, especially to the patient, will be obvious.

Acknowledgements.

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MEGAVOLTAGE RADIOTHERAPY.

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A NUMBER of institutions in Australia have installed megavoltage equipment and others have such equipment on order. This paper will present reasons why megavoltage equipment is an essential part of any good radiotherapy organization and what factors govern the type and energy of the equipment to be selected.

Reasons for Requiring Megavoltage Equipment.

The first physical advantage of megavoltage X-rays is their greater penetration, and Figure I shows the relative depth-dose curves for a variety of X-ray equipment. Thus the delivery of adequate tumour dose at a depth can be carried out much more effectively when megavoltage radiation is available. For example, from Figure I it will be seen that the dose at 10 cm. depth in tissue is, at 4 MeV, over 60% of the maximum dose, while at 250 K.V. the dose at the same depth is only a little over 20%. It should be noted that, because of the way in which the radiation interacts with the tissue, with megavoltage X rays the dose rises initially and the dose on the skin is thus very low. For example, at 4 MeV the skin dose is about one-third the maximum dose, and at a depth of 10 cm. the dose is still twice the skin dose. There are disadvantages in the use of too high an energy, and it will be seen from Figure I that the dose at 12 cm. depth at say 30 MeV is still much higher than the incident dose. Thus, for example, for a lateral field applied to a neck, the dose on the exit side for very high voltages is greater than that on the entry side.

The second physical advantage of megavoltage X rays relates to the way in which energy is deposited in different tissues. The energy absorption in bone relative to soft tissue changes fairly rapidly with X-ray energy up to a little under 1 MeV, but with energies above this level, there is very little difference between the energy absorbed in bone and that in soft tissue (Figure II).

At lower energies of the order of 200 to 250 K.V., the energy absorbed in bone is some two to three times that absorbed in soft tissue. It follows, therefore, that treatments carried out in the neighbourhood of bony struc-

tures can be given with less damage to the bone involved by using megavoltage radiation. Many common clinical problems may be cited as illustrations of these physical advantages. For example, in the radical treatment of a tumour of the floor of the mouth, skin reaction will require little attention but, of much greater importance, the serious complication of late radio-necrosis of the mandible may be expected to become much less common.

It is this latter consideration which gives the smaller teletherapy unit a place in the armamentarium of radiotherapy centres. By this is meant units employing tens rather than thousands of curies of radioactive material.

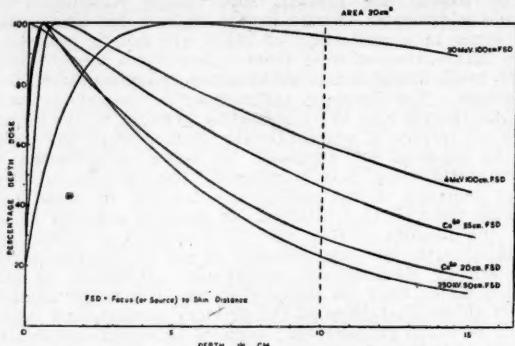


FIGURE I.

The radioactive materials with suitable characteristics which are available emit γ rays with energies equivalent to those from an X-ray set working in the 1 to 3 MeV range. To get usable dosage rates for quantities of radioactive material of this order, it is necessary to work at short source-skin distances of around 10 to 20 cm. compared with 50 to 100 cm. used with larger equipment. Small units of this type employing radium have been

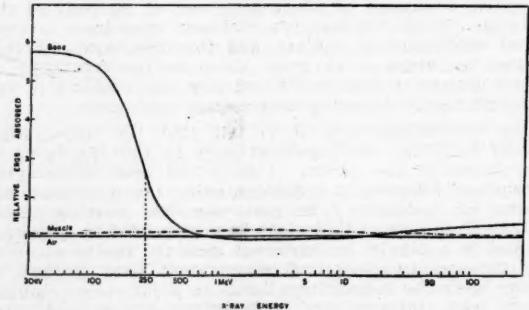


FIGURE II.

common in Britain and the European Continent for many years, and the ready availability, in recent years, of sources of a number of isotopes has given them new importance. With sources such as radium or cobalt 60, the distributions obtained at these short distances do not differ greatly from those obtainable with 250 K.V. X-ray plants (Figure I), but the high energy radiation, reducing as it does the energy absorption in bone and the dosage to skin, is a great advantage.

These units, with the comparatively small area fields which they cover uniformly, have been used effectively for lesions about the head and neck; a particularly favoured example is the treatment of carcinoma of the larynx.

Choice of Energy.

The highest γ -ray energy available with radioactive sources of practical use is equivalent to an X-ray set

operating at about 3 MeV, but higher energies than this can be obtained from electrical generators producing X rays. In so far as the higher the energy of the radiation the more penetrating it will be, it might seem reasonable to choose the highest energy available practically. However, there are some reasons which indicate that an energy of somewhere in the neighbourhood of four million volts represents an optimum. First of all, beams of high energy X rays do not provide a uniform dose rate across their width, the dose rate being highest in the centre and falling off more or less rapidly towards the edge. This is an unavoidable consequence of the way in which X rays are produced when the electrons hit the target. As the energy of the electrons is increased, so the X rays produced tend to be more and more in the direction in which the electrons were travelling when they hit the target. This results in the emergent X-ray beam being concentrated in a cone of decreasing angle with increasing energy. The distributions across X-ray beams of two energies are shown in Figure III. From

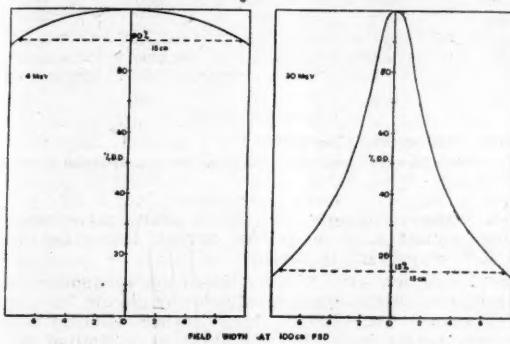


FIGURE III.

this it will be seen that the width decreases with increasing energy, and in order to use such high energy beams in therapy, it is necessary to filter the beam differentially (i.e., heavy filtration in the centre and thinner filters towards the edge) to produce uniform dose rate over a width of some centimetres.

From Figure III it will be seen that for a 4 MeV beam, a reduction in the intensity at the centre of some 10% will yield a uniform field nearly 15 cm. wide. Thus, the unfiltered output of the unit to give 200 r per minute need only be about 220 r per minute. At 30 MeV, in order to obtain a field 15 cm. wide, the necessary differential filtration would reduce the intensity at the centre by 85%. In order, therefore, to yield a flat field with a dose rate of only 30 r per minute, a 30 MeV unit would need to have an unfiltered output of 200 r per minute. Thus, for two units, one working at 4 MeV and one at 30 MeV, both giving, in conditions for treatment, 200 r per minute at 1 metre, the former would require an unfiltered output of 220 r per minute and the latter one of about 1300 r per minute. The special importance of providing these large uniform fields without undue sacrifice of dose rate can be illustrated by reference to clinical conditions where fields measuring 10 x 20 cm. or larger are common.

As a basis of comparison for the clinical distributions likely to be obtained, a hypothetical tumour at the centre of a 30 cm. diameter body has been considered. This has been irradiated by a number of X-ray beams whose contributions will add at the tumour. Such summations can be carried out for beams of various energies, and in Figure IV the result of doing this for three fields is shown. In Figure IV the skin to tumour dose ratio against energy is plotted. Our desire is for a low ratio of skin to tumour dose, and it will be seen that, while there is a fairly rapid improvement in this ratio up to about 2 MeV, the change thereafter is relatively slow, so that from this point of view an energy somewhere between say 2 MeV and 8 MeV is a reasonable choice.

Finally, if we return to Figure II and look at the variation of the relative energy absorption in bone and tissue, we will see that it stays in an approximately equal ratio, from about 1 MeV up to something over 15 MeV after which, because of the incidence of another means of energy absorption known as pair formation, the relative energy absorption in bone as compared with tissue goes up. Summing up the requirements gives the following situation. Good penetration is desired, but not so great that emergent dose becomes of concern. Build-up of dose below the surface is required to spare the sensitive skin, and the energy of the X rays should be such that the energy absorption in bone relative to soft tissue is low. It is also desired to work in an energy region, giving low skin to tumour dose ratios for multiple fields, and finally a good dose rate over large fields is necessary. These considerations indicate that a unit operating between about 2 and 8 MeV would be a good choice.

Choice of Type of Generator.

In the range above 2 MeV, the following types of generator are available as distinct from those which can

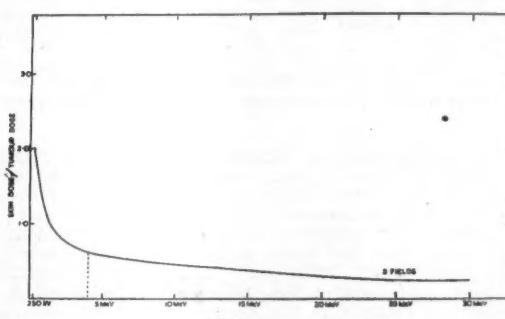


FIGURE IV.

be made to special order: (i) the resonant transformer operating at 2 MeV; (ii) the Van de Graaff generator operating at 2 MeV; (iii) the linear accelerator operating at 4 MeV; (iv) the betatron and synchrotron, in the range from about 10 to 70 MeV; (v) cobalt-60 teletherapy units with an equivalent peak energy of about 3 MeV.

Previous comments have indicated that we should confine our interest to the 2 to 8 MeV range, and this reduces us therefore to considering the resonant transformer, the Van de Graaff generator, the linear accelerator and the cobalt-60 units.

In order to assess the relative merits of these various units, an analysis, based on a method developed by Flanders, has been carried out and is presented in Table I. The analysis takes a standard condition, that of the delivery of 5000 r at a depth of 10 cm. in tissue, and assesses the number of patients who can be treated *per annum*, and the cost of treatment of a patient, including such things as the depreciation on plant and building, the cost of spares, and the cost of the operating staff. The actual figures in Table I should, of course, not be taken too literally for circumstances will modify the result obtained. For example, the building costs will be affected materially, depending on the availability of a clear site, on the necessity for adaptation of existing buildings or the installation in a confined site, while the turnover of patients will be affected by the treatment methods adopted. It will be apparent that a high output combined with a penetrating radiation will enable a large number of patients to be handled, and will offset the large capital investment in the unit and its housing. In fact, the cost per patient treated with most of the megavoltage units does not differ greatly from that with conventional 250 K.V. equipment. It will be seen that

TABLE I
Analysis of the Relative Merits of Various Types of Generators.

Observation.	Type of Unit.							
	250 kV.	2 MeV. Resonant Transformer.	2 MeV. Van de Graaff.	4 MeV Linear Accelerator.	24 MeV Betatron.	31 MeV Betatron.	Large Cobalt Unit. ¹	Medium Cobalt Unit. ²
Source-skin distance (cm.)	50	100	100	100	100	100	60	50
Dose rate (r/minute):								
Maximum .. .	—	—	—	—	—	—	55	58
Minimum .. .	—	—	—	—	—	—	38	39
Average .. .	35	100	75	200	40	25	46	48
Percentage depth dose at 10 cm.	36.2	54	54	62.7	80	95	52	49.6
Treatments in seven hours	20	30	27	35	21	16	22	21
Number of patients given 5000 r at 10 cm. in 260 days .. .	150	337	304	456	360	316	238	216
Capital cost (£A), including								
source	7000	75,000	36,000	70,000	80,000	45,000	36,000	16,000
Building .. .	3000	40,000	25,000	30,000	25,000	25,000	10,000	7000
Depreciation, 10% plant + 5% building .. .	850	9900	5000	8500	7200	3800 *	3800	1700
Annual cost of source .. .	500	400	2000	1500	1500	1000	900	1500
Spares and servicing .. .	200	200	500	600	600	300	100	80
Staff .. .	1500	1500	2000	2000	2000	1500	1500	1500
Total annual cost (£A) .. .	3100	11,700	5000	12,000	10,400	6600	6200	4780
Cost per patient treated (£A) .. .	21	34	19	26	32	21	26	22

¹ Source strength approximately 1500 curies. Working period taken as three years. Sources can be reactivated.

² Source strength approximately 800 curies. Working period taken as three years. Sources cannot at present be reactivated and new ones must be bought.

the 4 MeV accelerator compares favourably in relation to treatment capacity and costs with any of the other units; 4 MeV linear accelerators at present available employ so-called isocentric mounting. In this arrangement the "tube" moves in an arc around the patient in such a way that the beam is always directed towards a fixed focal point. This point is the normal treatment distance. It is located 100 cm. from the focus and is on the axis of rotation of the machine. The treatment table is an integral part of the unit, and is designed to move on a vertical axis through the same point, giving fundamental advantages in reproducing planned treatment arrangements on patients many times during a course of therapy. In addition, the source of the radiation or focal spot of the accelerator is small, and this together with a collimating system of good fundamental design means that the X-ray beams have sharply defined edges with a little or no penumbra. Cobalt units in general are rather poor in this respect, since the source diameters vary between 1.5 and 3 cm. according to requirements. A small focal spot also provides the very useful advantage that it makes possible the simple production of "positioning" and "checking" radiographs as a routine measure. Contrast between bone and soft tissue is, of course, minimal, but the presence of air in nasal accessory sinuses or lung, for example, and the relative absence of side scatter of this type of radiation allow for quite satisfactory diagnostic quality in the films.

It is concluded that the linear accelerator, at an energy of 4 MeV, represents perhaps the optimum type of unit for a large institution such as that with which we are connected. A linear accelerator, however, is a complicated piece of equipment and requires regular maintenance. Simpler maintenance, together with the low capital investment involved, makes certain cobalt teletherapy units attractive investments for centres serving smaller populations.

Because of the large source size associated with cobalt units containing sources of activity around 2000 curies, the use of cobalt 60 at modest source-skin distances around 40 cm. should be considered. Units of this type can accommodate approximately 1000 curies and are relatively cheap. They have a source of not too large a size, and working at around 40 cm. distance give reasonably good depth dose. They can do a very useful job, either on their own in a small community or as part of the armamentarium of a large centre, possessing

say a linear accelerator, but where additional equipment giving radiation of a quality harder than that from 250 K.V. equipment is desired.

In closing we wish to draw attention to another type of radiation beam made available by recent technical development. This is the high energy electron beam. Electron beams have the advantage of a limited range in tissue, after which the dose falls rapidly to a very low value (Figure V). The application of such distribu-

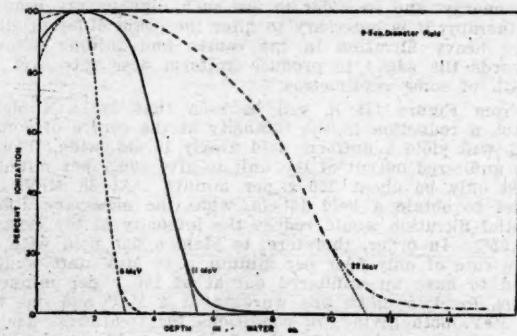


FIGURE V.

tions in the head and neck region where it is desired to treat a tumour close to one side and to spare structures in the mid-line will be obvious. An example might be the treatment of metastases in cervical lymph nodes, where the estimated depth for delivery of the chosen dose is 5 cm., and it is desirable to avoid high irradiation of the structures across the mid-line. Reference to Figure V shows that by choosing an energy of about 15 MeV, such a distribution would be easy to obtain. Again, treatment of the internal mammary nodes calls for delivering a dose at a depth of about 2 cm. falling off rapidly beyond this to avoid underlying structures. An electron beam of about 6 MeV would do this admirably.

As will be seen from Figure V, the sharp fall in dose beyond a certain distance becomes less marked as the energy increases. It is considered that there would be little advantage in beams of energies above say 25 MeV.

CARCINOMA OF THE BREAST TREATED WITH THIO-TEPA.

By H. HOLDEN AND B. SUNDSTRUP,
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A PRELIMINARY REPORT on five cases of carcinoma of the breast treated with thio-TEPA, with and without androgens, will be presented.

The first reported use of thio-TEPA was by Shay *et alii* (1953). They used it mainly in leukaemia, but they mention its use in two cases of advanced breast cancer. Our work was stimulated mainly by the work of Morales *et alii* (1958) on the use of nitrogen mustard or thio-TEPA to prevent the dissemination of metastases at operation. More recent work with thio-TEPA in breast cancer, by Bateman and Carlton (1956), Moore and Pickren (1958) and Watson and Turner (1959), has indicated that some effects can be achieved by this agent in breast cancer.

In view of the toxicity encountered with this drug, a preliminary report at this stage, even with few cases, was thought worth while.

Fluoxymesterone.

Sublingual methyl testosterone, intramuscular testosterone propionate and pellet implants of the latter are well-tried androgens. A report by Kennedy (1957) has shown that fluoxymesterone was five to ten times as potent as the propionate and was effective by mouth. More recently, Buckle (1959) has shown that the fluorinated preparation is seven to fifteen times as potent as the methyl compound. Stoll (1959) has given a concise review of the use of the "Halotestin" brand of fluoxymesterone in advanced breast carcinoma. Figure I com-

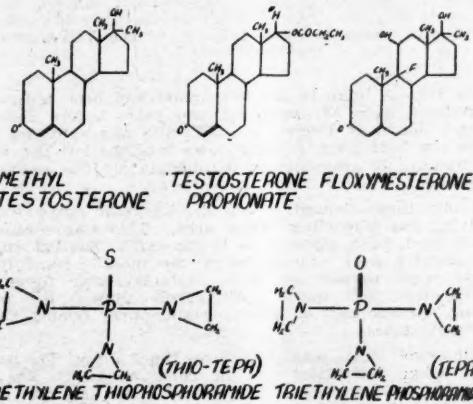


FIGURE 1.

pares the formulae of methyl testosterone, testosterone propionate, fluoxymesterone, thio-TEPA and TEPA.

As a result of the findings of the above-mentioned authors, it was decided to treat two patients with bony metastases with "Halotestin". These two patients were treated for six months before control began to fail, and they were the first patients to be treated with thio-TEPA.

Thio-TEPA.

Thio-TEPA has been developed from TEPA by the substitution of the oxygen radical for one of sulphur. Extensive animal experiments have been undertaken, with the use of ³⁵P labelled TEPA. This has shown that there appears to be no specific localization of radioactive material in any animal tissue examined, even when transplanted tumours have been inhibited by it. Of the given

dose, 80% was excreted in 24 hours. It can be assumed that thio-TEPA will behave in a similar way, but sulphur may be a more efficient radical to carry the compound to the unknown cell components vital to cell division, which are affected by the alkylation properties of the ethylene-immonium groups released there.

Selection and Assessment.

When orthodox palliative treatment by surgery or radiotherapy was normally indicated, then these methods were used in preference to chemotherapy, and in no case has thio-TEPA been the primary method of treatment. All cases were practically moribund, with widespread disseminated disease throughout the bony skeleton. All patients were either post-menopausal or had received a sterilization dose of X-ray therapy some time before. In some cases blood transfusion was necessary when the blood picture was depressed—below 9 grammes per 100 ml. of haemoglobin—before treatment. No cases have been encountered as yet in which there was an initial low white cell or platelet count, but this would be a bar to treatment without prior attempts to correct this state.

CASE I.—A woman, aged 71 years, presented herself in September, 1952, having noticed a lump in her left breast for two months. Examination revealed a hard lump 5 x 2 cm. in the upper outer quadrant of the left breast, which was attached to the skin, but not to deeper structures. Radical mastectomy was performed, and at operation involvement of the axillary lymph glands to the apex was found. The pathologist reported sclerous adenocarcinoma, with metastases in the glands. A course of deep X-ray therapy was delivered to the axilla. At that time, several small glands were noted in the left supraclavicular fossa, but these were regarded as insignificant.

The patient remained well with regular follow-up. In 1956, one of the supraclavicular glands was removed for histological examination. This was reported by the pathologist as "sinus catarrh". These glands continued to increase in size, and in May, 1956, another biopsy specimen was taken and this showed invasion by adenocarcinoma. Deep X-ray therapy was administered to the left supraclavicular fossa and the remaining glands regressed.

In November, 1957, she began to suffer from severe low back pain and weakness of the legs. Examination showed signs of an early developing paraplegia. X-ray films showed metastases in the eighth, ninth and tenth dorsal vertebrae, which were of osteolytic and osteoblastic type. Cobalt therapy was administered to the spine, and in four to five days marked symptomatic improvement was evident.

In August, 1958, the patient again began to suffer from right-sided back pain, radiating down into the leg. The pain responded to "Phenylbutazone" and fluoxymesterone, 40 mg. daily.

In October, the patient was operated on for perforated peptic ulcer. The phenylbutazone and "Halotestin" were ceased. "Halotestin" was reinstated at the beginning of November. The condition of the patient deteriorated, and the pain became more severe in her back and legs. Ambulation became more and more difficult. She was admitted to hospital in February, 1959, in a bed-ridden state and in considerable pain, relieved only by morphine.

Skiagrams showed extension of the metastases to the spine from the eighth dorsal to the fifth lumbar vertebrae. The whole of the pelvis was involved, and metastases also were present in the upper parts of both femora.

She was still taking fluoxymesterone. This was ceased. A course of thio-TEPA, totalling 90 mg., was administered intravenously over 10 days (Figure II A). In the following two to three weeks, the pain was almost completely relieved, and the patient again became ambulant. The blood picture showed considerable depression of the bone-marrow elements, but did not cause any symptoms. Cortisone and dienestrol were given to restore the blood picture and were ceased when this returned to normal and "Halotestin" was substituted.

Check skiagrams showed a halting of the metastatic process in the spine and pelvis and a marked regression in the lesions in the heads of the femora.

In April, 1959, another course of 80 mg. of thio-TEPA (intramuscularly) was given over five days and the fluoxymesterone continued (Figure II B). At the present time

(July) she remains symptomatically well. She has put on weight, and can move about reasonably well without discomfort. She is taking 40 mg. of fluoxymesterone daily; when she was readmitted to hospital for further thio-TEPA, X-ray examination of the chest showed several metastases in the lung fields. She is having a further course of thio-TEPA.

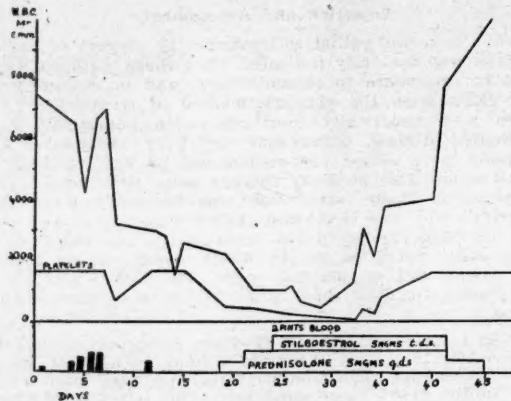


FIGURE IIIA.
Case I: treatment with 90 mg. of thio-TEPA given intravenously.

CASE II.—In November, 1956, the patient, aged 54 years, underwent left radical mastectomy. Pathological examination showed a scirrous carcinoma with spread to the axillary lymph glands.

The patient remained well until March, 1958, when she began to suffer from low back pain, which radiated down

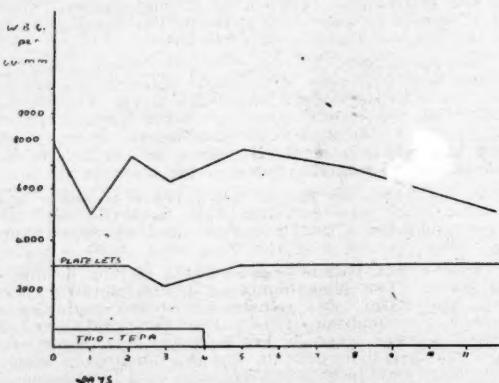


FIGURE IIIB.
Case I: treatment with 80 mg. of thio-TEPA given intramuscularly plus 40 mg. daily of "Halotestin".

the medial side of the thighs. Skigrams showed secondary metastases in the fifth lumbar vertebrae and left ischium. Palliative cobalt beam therapy was administered to these secondary metastases with some effect. Skigrams taken in August showed extension of metastases in the pelvic bones, and another secondary deposit in the left tibia. The area treated by cobalt gamma radiation remained sclerosed. Fluoxymesterone, 40 mg. daily, was begun, and this gave considerable relief of pain. Skigrams taken in October showed rapid extension of metastases to all of the lumbar vertebrae, the eighth and tenth dorsal vertebrae and in both eighth ribs. Pain remained fairly well controlled with fluoxymesterone, and the patient was reasonably ambulant.

In February, 1959, the patient was readmitted to hospital in considerable pain and bed-ridden. She was no longer responding to the fluoxymesterone. This was ceased, and an heroic course of 147 mg. of thio-TEPA was given intra-

venously over eleven days (Figure III). Fluoxymesterone was begun again, when the course of thio-TEPA was completed. She was discharged from hospital, and felt much more comfortable. Six days later the patient was readmitted to hospital with severe epistaxis. Examination of the blood showed extreme depression of all cellular components of the blood. After seven pints of fresh blood, 250 mg. of "Honvan" given intravenously, stilboestrol and prednisolone, the patient rapidly recovered, and the blood picture returned to normal. The patient no longer suffered from pain, except in her right hip, on movement.

The patient was readmitted to hospital in July for another course of thio-TEPA. Skigrams showed extension of the bony metastases. She had a pectrochanteric fracture of the right femur; the eighth thoracic vertebra had collapsed and the right eighth rib and left twelfth rib were severely involved. She was very cheerful and suffered only from mild pain in the right leg and hip.

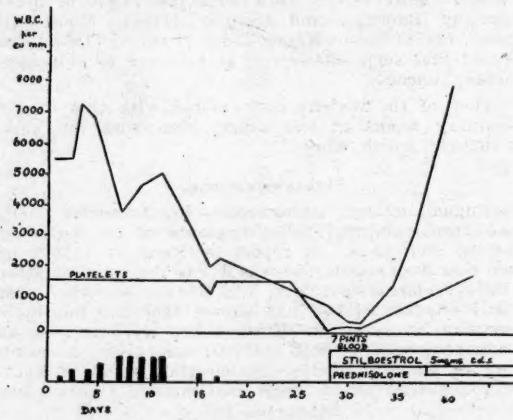


FIGURE IIIC.
Case II: treatment with 147 mg. of thio-TEPA given intravenously.

CASE III.—A lump in the left breast had been noticed by the patient, aged 54 years, for two years before she consulted a doctor in December, 1958. She was suffering from severe low back pain, passing down into the left leg, which was making it gradually more difficult for the patient to move about.

Examination showed a hard, irregular, fixed mass, involving the whole left breast area. This was continuous with a hard, fixed, gland mass in the axilla. Several satellite skin nodules were present below the mass. Hard lymph glands were present in both supraclavicular fossae and also in the right axilla. Skigrams showed the pelvis, sacrum, lumbar part of the spine and upper femora riddled with metastases.

Stilboestrol, 5 mg., was given three times a day. The patient had become bedridden and in constant pain. She was miserable and depressed. The use of a bed pan and movement in bed caused much pain. She was taking large doses of "Marsilid", chlorpromazine and morphine. By mid-February, 1959, she was taking one-sixth of a grain of morphine every four hours.

In April, skigrams showed progression of the bony metastases and a fracture of the neck of the right femur. Some regression of the lymph glands in the supraclavicular fossae and axilla had occurred. The main tumour mass and satellite nodules were unchanged.

Stilboestrol was ceased, and fluoxymesterone, 40 mg. daily was begun. A course of 80 mg. of thio-TEPA given intramuscularly over five days was given (Figure IV). Clinical improvement began immediately. In June, another similar course of thio-TEPA was given.

At the present time (July) the patient has no pain, apart from that due to her fractured femur. She no longer takes any morphine, chlorpromazine, etc. She has put on 13 lb. in weight and eats ravenously. If it were not for her fractured femur, she could be fully ambulant. Check skigrams of the bony metastases suggest that their growth has not been checked.

CASE IV.—After noticing a lump in her right breast for one year, the patient, a single woman, aged 58 years, underwent radical mastectomy in November, 1956. A scirrhouous carcinoma was found with involvement of the axillary lymph glands. A course of post-operative deep X-ray therapy followed.

The patient remained well until approximately February, 1959, when she began to suffer from low back pain, and she went to the doctor. Skiagrams showed extensive involvement by metastases of the lumbar part of the spine and metastases in the lung fields. The liver was stony hard and enlarged to 3 in. below the costal margin.

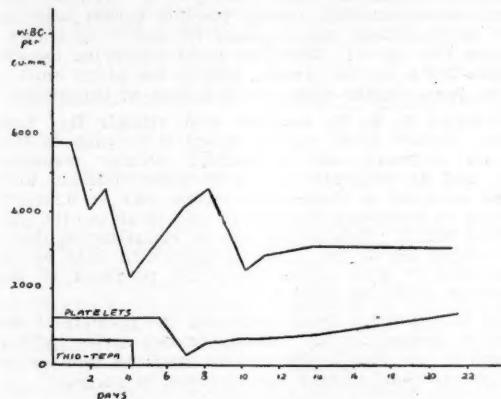


FIGURE IV A.

Case III: treatment with 80 mg of thio-TEPA given intramuscularly.

In April a course of 80 mg. of thio-TEPA was administered over five days (Figure V). The patient did not respond, but sank quickly into hepatic coma, although her pain was completely relieved. No "Halotestin" was used in this case. Permission for an autopsy was not granted.

was present in the right breast above the nipple. There were hard glands in the left axilla and left supraventricular fossa. Skiagrams showed suspicion of pelvic metastases and involvement of the fourth left rib and seventh right rib posteriorly. A sterilization dose of X-rays to the ovaries was given.

In March, fluoxymesterone, 40 mg. daily, was begun.

In May, skiagrams of the bony metastases suggested improvement and some recalcification.

The patient was admitted to hospital in June, in a rundown state. She was suffering from low back pain, left-sided

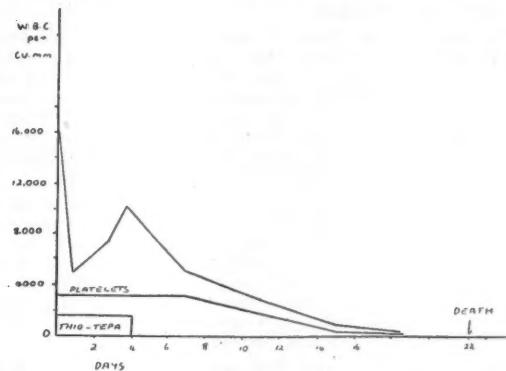


FIGURE V.

Case IV: treatment with 80 mg. of thio-TEPA given intramuscularly.

chest pain and breathlessness. A left-sided blood-stained pleural effusion was present. This was aspirated and 6 mg. of "Lekamin" were instilled to prevent recurrent effusion. This manoeuvre so far is quite satisfactory.

A course of 85 mg. of thio-TEPA was given intramuscularly in five days, the fluoxymesterone being continued throughout the whole period (Figure VI). A further

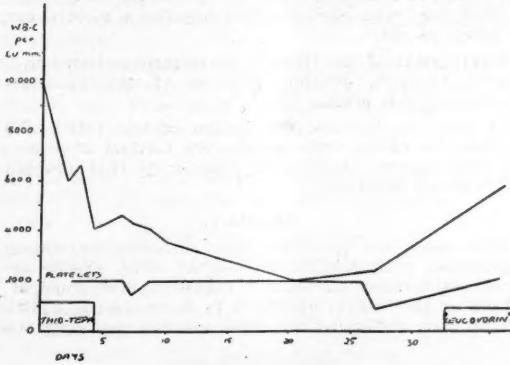


FIGURE IV B.

Case III: treatment with 80 mg. of thio-TEPA given intramuscularly plus 40 mg daily of "Halotestin".

CASE V.—In 1955, the patient, aged 33 years, noticed a lump in her left breast. This was removed, and the pathologist reported "chronic mastitis, with some areas approaching malignancy". Simple mastectomy was performed. Examination of the specimen revealed lobular hyperplasia, but no malignant disease was seen.

In 1957 the patient became pregnant, and noticed enlargement of glands in the left axilla. These regressed again after the puerperium. She remained well until January, 1959, when she began to suffer from low back pain and general loss of energy and weight.

On examination, several small nodules were found at the upper end of the mastectomy scar. A hard mass 5 x 2 cm.

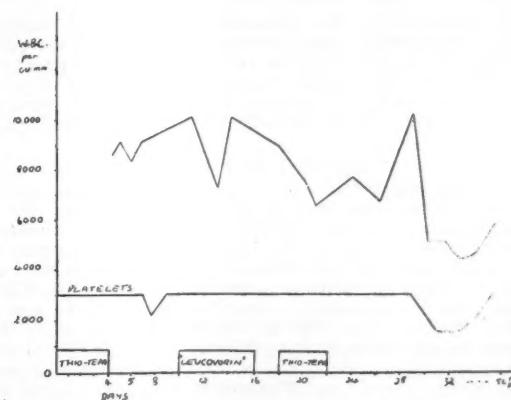


FIGURE VI.

Case V: treatment with thio-TEPA given intramuscularly plus 40 mg. daily of "Halotestin".

course of 85 mg. given intramuscularly in five days followed two weeks later.

Her general condition is now much improved and she has no pain. The skin nodules and the enlarged lymph glands are still present, but are regressing. The mass in the right breast is half its former size.

Haematological Changes.

Figures II A and III show the profound depressant action of thio-TEPA on the cellular elements of the peripheral

blood; in these two cases 90 and 147 mg. respectively of the drug were given intravenously. This route was chosen to obtain as rapid a response as possible, so that the depressant effects could be assessed without the confusing delayed effect that might result from intramuscular administration. However, these effects appear within a few days as far as the leucocytes are concerned, and appear to reach a maximum between the twenty-first and thirtieth days whichever route is used. It is also interesting that a transitory fall in the platelet level appears to precede the maximum leucocyte depression, but at a variable time. This we have found also occurs regularly in patients we have treated with mannomustine for differing conditions.

The patients in Cases I and II were not receiving "Halotestin" during their first course of thio-TEPA. They had received 40 mg. of this androgen per day for the immediately preceding six months. These first two cases treated illustrate clearly the ease with which thio-TEPA will destroy the marrow elements. Recovery was stimulated in these two cases with prednisolone and stilboestrol given by mouth and with fresh blood transfusions.

Stilboestrol dipropionate will afford some protection to the bone marrow during whole-body radiation as reported by Bellesia *et alii* (1957), and we have confirmed this in some of our own cases undergoing whole-body X-ray therapy. It appears to have had a dramatic effect in the above-mentioned two cases. "Honvan" given intravenously (one dose of 250 mg.) was used in Case II to stop a serious epistaxis and had immediate effect.

Figures IIa, IVa and IVb and VI show clearly some protective effect due to the concomitant "Halotestin".

Figure V shows the result of another case unprotected by "Halotestin" and with gross liver involvement. It is possible that the deamination function of the liver may render inactive the ethylenimonium compounds released from the thio-TEPA.

Even with the protection of "Halotestin", profound toxic effects on the bone marrow cellular elements are produced, as shown by the peripheral blood picture in Figure IVa. Figure VI shows two courses at a two-week interval. This was perhaps achieved by the use of citrovorum factor (folic acid; *vide infra*).

In summing up the haematological findings, it appears that "Halotestin" does protect the erythroleucopoietic powers of the bone marrow to some extent. Even if profound depression occurs, recovery with cortisone and stilboestrol is possible, although we would not like to have to repeat our experience with the first two cases.

Reactions to Treatment.

No side effects of a complicating nature are encountered when bone-marrow depression is excluded. No patient complained of nausea, vomiting or anorexia. A consistent observation by both of us independently showed that the patients, although not drowsy, slept well both day and night. They all showed a feeling of general well-being and almost approached a condition of euphoria towards their illness. This was in remarkable contrast to their state on admission to hospital.

Discussion.

All patients showed remarkable relief of pain within four days of commencing thio-TEPA. The first two patients had relapsed into pain after control with fluoxymesterone for six months, so that there is no doubt in these cases that relief of pain was due to thio-TEPA. All patients were so relieved that the heavy sedation previously necessary was reduced to an occasional oral dose of a mixture containing morphia and aspirin. Three of the five patients became ambulant and returned home.

The character of the bony metastases has altered little in all cases, and is extensive. In two cases there has been evidence of substantial regression of soft-tissue masses.

The degree of bone-marrow depression in our cases may be due to the considerable amount of marrow replaced by

malignant infiltration, and we await the result on three further patients now under treatment, in whom there is no extensive involvement of bone.

Apart from the use of androgen to protect the marrow, it is possible to do so with oestrogen, and we see no reason in the future, if we have a case with soft-tissue involvement only, why the androgen could not be replaced by stilboestrol dipropionate.

The main problem is to interfere with the effect of the agent on the bone marrow, whilst retaining its effects on the tumour cells. With this in mind, we have now instituted treatment with "Leucovorin" (folic acid) given intramuscularly. Some possible benefit may have been obtained from this in Cases III and V, as shown in Figures IVa and VI. To try to avoid destroying the effect of thio-TEPA on the tumour, this is not given until two weeks have elapsed since the last dose of thio-TEPA.

Vitamins B₁, B₂, B₆, nicotinic acid, vitamin B₁₂, "Leucovorin" (folic acid) and all essential enzymes in tissue oxygen exchange, and presumably cellular metabolism also, and an adequate supply of these vitamins known to be essential to leucocythropoiesis may be a selective method of protecting the marrow and retaining the effects of thio-TEPA. This is the line of investigation that we are taking up, as the doses of thio-TEPA that we have been able to give so far have not produced as much effect as might be desired.

We have not yet been faced with the problem of maintenance dosage, as the patients in our series have proceeded to the full five-day course again as soon as their peripheral blood picture has returned to normal.

Conclusions.

Thio-TEPA is very toxic to the leucocythropoietic tissues.

The dramatic improvement in the general condition of the patients treated makes further trial by this agent necessary.

Regression of soft-tissue primary and secondary metastases has occurred in two cases, but a further case has developed pulmonary secondary metastases whilst awaiting the return of a normal blood picture before another course of treatment was started. Too hopeful a picture cannot be given as yet.

Involvement of the liver by metastases appears to be a special problem, possibly because of the deamination function of this organ.

In order to increase the dosage of thio-TEPA and to increase its effect, some satisfactory method of protecting the bone-marrow elements in addition to that afforded by androgen is necessary.

Summary.

Five cases are presented with advanced carcinoma of the breast treated with thio-TEPA. The effects on the blood cell-forming tissues are tabulated, and some of the effects on the tumour appear to be encouraging. Additional methods of protecting the bone marrow are suggested.

Acknowledgements.

We wish to express our thanks to Dr. L. N. Gollan and Mr. D. McIntyre for referring cases, and to Dr. L. Manoim and Mr. F. J. Brown, of the Pathology Department of the Launceston General Hospital, for haematological studies. The thio-TEPA was provided by the Lederle Division of the Cyanamid Corporation of the United States, to whom our thanks are due.

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THE MANAGEMENT OF HYPNOTIC OVERDOSAGE.

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OVER the past decade, several large series of cases of barbiturate overdosage have been published (Nilsson, 1951; Reed *et alii*, 1952; Clemmensen, 1954; Plum and Swanson, 1957). These reports, however, have generally emanated from special units specifically dedicated to the treatment of this condition. It was therefore thought that it might be of interest to see what sort of results could be obtained from a large and busy general hospital.

The present report is based on a series of 649 consecutive patients suffering from overdosage with a hypnotic drug, who were admitted to the adult wards of the Brisbane General Hospital during the period July, 1953, to June, 1957. The series is not restricted to cases of barbiturate overdosage (though these formed 90% of the series) as the management of all varieties of hypnotic overdosage is essentially similar.

Analysis of Series.

Of the 649 patients in this series, 44 were admitted to hospital on more than one occasion because of overdosage, so that there was a total of 755 admissions. Four patients who had died before being seen by the medical staff have been excluded.

The annual incidence showed a progressive increase, as follows: 1953-1954, 147; 1954-1955, 149; 1955-1956, 215; 1956-1957, 244. Thus there was a 60% increase over this period.

Sex.

In this series there were 403 females (62%) and 246 males (38%); of those who died, 53% were males.

Mental State of Patients.

The mental state of the individuals who took these overdoses was as follows:

Depression	36%
Hysteria	23%
Personality defect (neurotic or psychopathic)	20%
Acute alcoholism	8%
Schizophrenia	7%
Organic neurological disease	4%
Overdosage (accidental)	3%

Had there been more information available, it is probable that the number of cases of hysteria would have been increased at the expense of the group of neurotic and psychopathic personalities.

Purpose of the Overdose.

In endeavouring to elicit the purpose for which the overdose was taken, several difficulties were encountered. The information available might be inadequate; people might deny a suicidal intent when interviewed on the day after their overdose because they feared the legal and psychiatric implications of such an admission; people who

took a relatively trifling overdose for some hysterical purpose might find it later to their advantage to claim a suicidal intent; and people who took their overdose while alcoholic often did not remember the purpose of their actions when they awoke. An attempt is made to set out the purposes of the overdosages, in as far as it can be determined in the light of these considerations, as follows:

Suicide	61%
Relief of symptoms (including insomnia, 21%)	28%
Accident	4%
Temper tantrums	3%
For sympathy	2%
Addiction	2%

Types of Hypnotic Ingested.

Table I shows the frequency of ingestion that was encountered for each hypnotic. Information as to the dosage taken was so unreliable that it was considered that no valid result could be obtained by considering this aspect.

Alcoholism was associated with 17% of the admissions.

TABLE I.
Hypnotics Ingested and Death Rate for Individual Substances.

Hypnotic.	Number of Cases.	Percentage to First Decimal Place.	Death Rate. (Percentage.)
Unnamed barbiturate	171	22.8	4.7
Phenobarbital	213	23.4	5.1
Pento-barbital	188	25.0	2.7
Buto-barbital	26	3.5	—
Barbitone	31	4.1	16.0
Cyclo-barbital	3	0.4	—
Amylobarbital	9	1.2	11.0
Quinal-barbital	3	0.4	—
"Carbital" (carbromal and pento-barbital)	36	4.8	5.6
Phenytin	4	0.6	—
Primidone	2	0.3	—
"Relaxatals"	4	0.5	—
Chlorpromazine	5	0.7	—
Benzactin	1	0.1	—
"Mesantoin"	1	0.1	—
"Dordine"	1	0.1	—
Morphine	2	0.3	—
Hyoscine	1	0.1	—
Atropine	3	0.4	—
Paraldehyde	11	1.5	—
Potassium bromide and chloral mixture	27	3.6	7.4
Promethazine	2	0.3	—
Chloral hydrate	6	0.8	—
Antesolone ("Antistin")	1	0.1	—
Pethidine	1	0.1	—
Reserpine	1	0.1	—
Benzhexol	1	0.1	—
Mephenesin	1	0.1	—
Total	755	100	4.5

Severity of Cases.

From the point of view of comparison of results with those of other series, it is necessary to divide the cases into several groups. As it has been the practice of the hospital to admit all persons who have taken overdoses of hypnotics, it has been necessary to employ a fourth category of trivial cases over and beyond the categories of mild, moderate and severe, which I define similarly to Locket and Angus (1952) and Isabell (1955). The classification is as follows:

Trivial: no clinical effect.

Mild: drowsiness; perhaps impaired cerebration; patients can be aroused sufficiently to converse.

Moderate: stupor; patients can be aroused by painful stimuli, but not sufficiently to speak.

Severe: coma; depressed reflex and vegetative functions.

The composition of the series in terms of these criteria is set out in Table II.

Therapy Employed.

On their admission to hospital, all patients are assessed clinically, particular attention being paid to the level of consciousness, pulse, blood pressure, respiration and temperature. Records of observation on these are kept at from 15 to 60 minute intervals, depending on the assessment of the gravity of the case.

Initial gastric lavage was performed when the drug was believed to have been taken in the preceding three or four hours, and when the patient's physical state did not preclude such a procedure. In adopting this course, we have taken a course between the extremes of Clemmensen (1954), who never washes a stomach out, and Locket and

TABLE II.
Composition of Series in Terms of Severity of Overdosage.

Year.	Trivial.	Mild.	Moderate.	Severe.	Total.
1953-1954	30 (20%)	64 (45%)	31 (21%)	22 (16%)	147
1954-1955	21 (14%)	76 (51%)	32 (21%)	20 (14%)	149
1955-1956	33 (15%)	107 (50%)	48 (23%)	27 (13%)	215
1956-1957	44 (20%)	118 (47%)	47 (19%)	30 (12%)	244
1953-1957	133 (17%)	365 (40%)	158 (21%)	99 (13%)	755

Angus (1952), who believe that significant quantities of barbiturate can be removed from the body by lavage, no matter how late it is performed. Nevertheless, lavage is coming to be used less frequently, as can be seen from Table III.

TABLE III.
Methods of Treatment and Fatalities, by Years (Percentage of All Cases).

Method.	1953-1954.	1954-1955.	1955-1956.	1956-1957.
Gastric lavage	71	51	26	33
Parenteral fluid administration	6	20	20	16
Chemotherapy	31	31	26	19
Picrotoxin or "Cardiazol"	23	8	7	2
"Mecamide" - amphetamine	0	2	1	3
Amphetamine and "Methedrine"	37	26	10	16
Deaths	6.0	3.3	5.0	3.7

Patients are nursed on their side with the foot of the bed elevated, and are turned every two hours. Whenever possible a nurse is in constant attendance. Oxygen is administered by intranasal catheter when indicated, and a pharyngeal airway and suction are employed if necessary. Endotracheal intubation was not used during the period under consideration, though a mechanical respirator was employed once, without success.

Prophylactic chemotherapy was used as shown in Table III, penicillin being the initial antibiotic administered. It was used less often over the years, because as gastric lavage was used less often there was less necessity to protect the patients against potential aspiration pneumonia induced by this procedure. The belief that prophylactic chemotherapy is pointless, simply allowing infection by resistant organisms to supervene, did not influence the figures; but in this connexion 70% of our patients who died and who had been unconscious for more than 24 hours were found at necropsy to have pneumonia.

As the principles of fluid therapy became more widely appreciated, fluids were given by the parenteral route more often (as Table III shows). This treatment is now employed for all patients who seem as though they will not be able to attain a reasonable oral fluid intake within 12 hours, or in whom there is, or seems likely to be, depression of vital functions. Vasopressor drugs were used to maintain the systolic blood pressure above 80 mm. of mercury; amphetamine and methedrine were used first,

and if they proved inadequate, mephentermine and noradrenaline.

The attitude towards the use of analeptics has followed, conservatively, the overseas trends (Table III). Especially in the latter period of the survey, amphetamine and methedrine were used as vasopressors rather than as cerebral stimulants. Because its use is complicated, and because it came on the scene as the swing against analeptics gathered momentum, the bemegride-amphetamine régime of Shulman and Shaw (1955) did not attain much popularity.

Results of Therapy.

The results which have been obtained by the use of the methods indicated are as shown in Table IV. From Table III can be seen some little tendency of the results to improve as analeptics were used less frequently.

TABLE IV.
Results of Therapy.

Year.	Number of Cases.	Deaths.	Death Rate (Percentage).			
			All Cases.	All Except Trivial.	Moderate and Severe.	Severe.
1953-1954	147	9	6.0	7.7	17.0	41
1954-1955	149	5	3.3	3.9	9.6	25
1955-1956	215	11	5.0	6.0	14.7	41
1956-1957	244	9	3.7	4.6	11.8	30
1953-1957	755	34	4.5	5.5	13.5	34

Autopsy Findings.

In half the fatal cases there was evidence of pneumonia (70% of patients who survived for longer than 24 hours), and in the majority of the remainder death seemed to occur by pulmonary oedema. The following list gives some indication of the associated conditions (percentage incidence in fatal cases) which were found at necropsy:

Coronary artery disease (severe)	21%
Cerebro-vascular disease (severe)	9%
Valvular heart disease	6%
Cirrhosis	3%
Tuberculosis	3%
Septicæmia	3%
Esophageal stenosis	3%
Ulcerative colitis	3%

Discussion.

In so far as the present local community is concerned, it can be seen that the problem of hypnotic overdosage is a growing one, with a 60% increase over a four-year period in which there was an 8% increase in the population of the city. During this period the annual number of admissions to hospital for non-hypnotic overdosage was relatively constant, being 41 ± 4 cases a year. Over the four years, hypnotics accounted for 82% of all cases of overdosage.

There is little in the psychiatric background of these patients that requires further comment, and the greater success of males than of females in destroying themselves is not surprising when one thinks of all the trifling hysterical overdosage cases that are encountered in females. It seems reasonably certain that the true incidence of attempts at suicide in these cases is higher than the figures indicate. This was also Hambourger's (1940) impression of the cases which he collected. The grounds on which this view is based have been indicated earlier.

Barbiturates comprised 90% of the hypnotics ingested, and of these, in the cases for which the type of barbiturate taken was known, approximately half of 87% of all such cases were instances of ingestion of phenobarbitone and half were instances of ingestion of pentobarbitone. This, no doubt, is merely a reflection of local prescribing

tendencies. It can be seen that the fatality rate for each variety of barbiturate was reasonable constant, with the exception of amylobarbitone, for which the number of cases was small, and of barbitone, the 16% mortality for which confirmed the evil reputation that local experience had attributed to this drug.

Over recent years there has been not inconsiderable controversy over the best type of management of these cases, and even now there is no unanimity of opinion. In looking back on the methods employed over the years, it is obvious that the necessity for adequate supportive and maintenance therapy has always been appreciated, and that additional methods which further these ends have been recruited as they became available.

About two decades ago analeptics were widely used in an endeavour to rouse the more severely affected patients, and at this time a mortality of 20% seems to have been the accepted figure (Nilsson, 1951). Koppanyi and Fazekas (1950) sought to define this line of therapy, and advocated a more restricted use of picrotoxin, employing this substance only in severe cases, in which recovery was unlikely on conservative management alone. The cases which met this criterion were those in which there was no response to a trial dose of picrotoxin. Reed *et alii* (1952) quoted improved results when analeptics were used with discrimination, and Dick (1952) advocated amphetamine as the analeptic of choice in place of picrotoxin, believing that with this latter drug there was a risk of inducing convulsions, control of which might necessitate further barbiturate administration.

Meanwhile, Nilsson (1951) claimed to have achieved a death rate of 2.3% in 176 severe cases managed without analeptics. This author pointed out the similarity between a patient suffering from barbiturate overdosage and an anaesthetized man, and suggested that the methods proved of value in the management of the latter should be the most successful for the former. Koppanyi and Fazekas (1952) took issue with certain of Nilsson's statements, mainly on a theoretical and pharmacological basis; they acknowledged that in most cases of overdosage recovery would occur with conservative management, but thought that there was a small group of severe cases in which they could salvage the patients by the use of picrotoxin in dosage kept below convulsive level. In 1954, Clemmensen of Copenhagen published a very large series which seemed as though it would sound the death knell for analeptic therapy—a death rate of 1.6% in 1276 cases.

Yet authorities in the United States were not entirely convinced. In 1956 Fisher and Freimuth advocated stimulant therapy almost as a routine, and eight months later Parker (1957) condemned the use of such drugs. From Seattle came Plum and Swanson's (1957) series with a 1.6% mortality in 243 cases managed conservatively. At about the same time Clemmensen (1956), who had advocated conservatism so strongly, saw fit to comment that the "Megemide"-amiphenazole combination of Shulman and Shaw (1955) seemed to have a place in therapy, if only for patients with severe respiratory depression.

It would, then, seem that, at present, in the majority of cases adequate conservative therapy is the wisest course; but there may perhaps be a place for stimulant therapy in special circumstances. Our experience has borne out the fairly well established fact that restriction of analeptic therapy will improve results. As can be seen from the description of the methods employed in this hospital (*vide supra*), no fixed policy has been followed, but a course between the extremes of the various enthusiasts has been adopted, with a gradual inclination towards conservatism.

While at first glance the mortality in severe cases in this series may seem a little surprising, there are several factors which warrant consideration. Of the 34 deaths, four occurred within two hours of the patients' admission to hospital, before a therapeutic régime could be organized properly. One of these patients, who died in nine hours, was primarily suffering from a myocardial infarction, and

the part that barbiturate played in his death is difficult to ascertain. Three regained consciousness only to die of pneumonia that was not controlled by chemotherapy. Thus, one-quarter of the fatal cases may well be excluded on these grounds. Now, from Figure I (which shows the survival times after admission to hospital for the present series, and for a composite series drawn from the literature in which such details were given), it may be seen that our fatality rate is higher for the first 24 hours, but after this the graphs are roughly parallel. While this high early mortality (39% in the first 24 hours, 61% by the end of 48 hours) could be attributed to inadequate therapy, the fact that this same therapy over the next five days tended to produce relatively better results seems to indicate that some other factor was operating. To some extent the patients instanced above who died soon after admission to hospital contribute to this; but there is probably another local factor which may load the series.

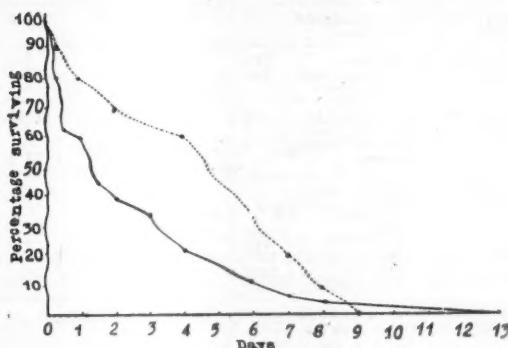


FIGURE I.

A comparison between the survival times from the patients' admission to hospital in the fatal cases in the series (solid line), and in similar cases from a composite series (interrupted line) drawn from the cases of Nilsson (1951), Locket and Angus (1952) and Plum and Swanson (1957).

Most authors now believe that in the majority of fatal cases the patient has some underlying physical disease, and this has been so in many of our cases (see list under "Autopsy Findings").

Table V shows an attempt to compare our results with those of overseas series. The evaluation of the different series is difficult, because there are almost as many classifications of severity of cases as there are authors, and the word "coma" can have quite an elastic meaning. Even when comparable criteria of severity are used, as in our cases and in those of Locket and Angus (1952), the proportion of the cases in each group may differ. In our series 58% of cases were mild, 25% moderate and 17% severe; yet for Locket and Angus (1952), comparable figures were 31%, 32% and 36%. Some series—e.g., that of Plum and Swanson (1957)—contain so high a proportion of severe cases that, while the cases may be consecutive, the hospital admission criteria must introduce an element of selection into the material. It is because of such factors as these, and because of the suspicion that our series may be somewhat loaded with poor-risk cases (as may be other series, of course) that comparisons between series are valid only in a very approximate sort of way. In the light of all these considerations, the results obtained do not seem unreasonable.

Summary.

Cases of overdosage of hypnotics are becoming increasingly frequent in Brisbane (60% rise over four years). The majority of these overdoses are taken by hysterical or depressed persons with suicidal intention, and 4.5% of these persons do die.

The changes in the management of such cases over a four-year period, and the results obtained thereby, have been indicated, and these results have been compared with those obtained elsewhere.

The development of therapeutic concepts has been discussed.

TABLE V.
Comparison of Results.

Author.	Nature of Series.	No. of Cases.	Mortality. (Percentage.)	Brisbane Series.	
				Comparable Cases.	Mortality Rate (Percentage).
Hamburger (1940).	All patients admitted to several hospitals.	643	7.3	755	4.5
Locket et alii (1952).	Mild, moderate and severe cases.	64	3.0	622	5.5
Plum et alii (1957).	(i) All cases .. (ii) Moderate and severe cases ..	243 160	1.6 2.5	755 257	4.5 13.5
Nilsson (1951).	Conscious and unconscious (two-thirds of series) patients.	176	2.8	Between 622 and 257	Between 5.5 and 13.5
Clemmensen (1954).	Probably mild, moderate and severe cases : 1948 .. 1949 .. 1950 .. 1951 .. Total, 1948-51	802 1041 1288 1276 4407	12.0 6.1 3.7 1.6 5.2	622	5.5
Reed et alii (1952).	Moderate and severe cases only (they include a few mild cases) : 1940 - 1949 (free analeptics). 1949 - 1951 (restricted analeptics).	192	14.6	257	13.5
		83	6.0	257	13.5

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THE SYDNEY FUNNEL-WEB SPIDER (ATRAX ROBUSTUS): II. VENOM YIELD AND OTHER CHARACTERISTICS OF SPIDER IN CAPTIVITY.

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It has been shown previously that the venom of the male *Atrax robustus* is considerably more toxic to laboratory animals than female spider venom, and that male spiders have less venom than female spiders (Wiener, 1957).

The results of further experiments have supplied additional data on the venom yield and other characteristics of *A. robustus* in captivity.

Source and Transport of Spiders.

A. robustus occurs commonly around the north shore of Sydney, and the assistance of local residents was enlisted to obtain a continuous supply of live spiders.

These were sent to Melbourne by air in screw-capped perforated plastic jars which contained a piece of moist cotton-wool (Figure I). During transport the spider

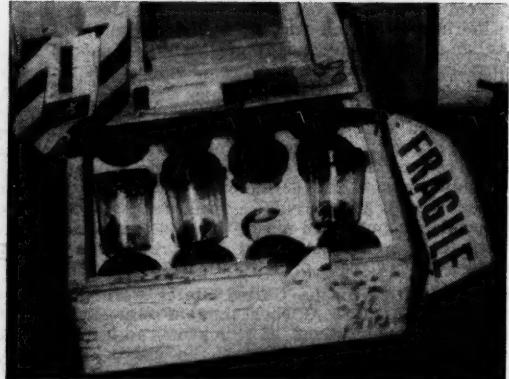


FIGURE I.
Plastic containers used for transporting *Atrax robustus*.

supported itself on the cotton-wool, which it transformed into a round or oval compact ball. In the laboratory each spider was kept in a screw-capped glass jar containing a layer of moist soil (Figure II). All female spiders were classified according to size as large, medium and small, and stored in cardboard boxes on wooden shelves on a balcony. Male spiders were also kept in separate boxes. Amongst the 3466 spiders which were received from July, 1956, to October, 1958 (Table I), 306 spiders were not *A. robustus* and belonged to other genera and families.

Venom Yield Obtained by "Milking".

Venom was collected from the fangs of spiders by means of a glass pipette with a fine tip and then freeze-dried. At each "milking" a record was kept of the number of spiders which yielded venom and the weight of venom obtained.

From July, 1956, until October, 1958, venom was collected on 73 occasions from female spiders of all sizes, and on 26 occasions from mature male spiders. The

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number of spiders "milked" on each occasion depended on the number available at the time. For the female group, it varied from 25 to 190, with an average of 65 spiders at each "milking". The number of male spiders milked on each occasion ranged from two to 23, with an average of 10 spiders.

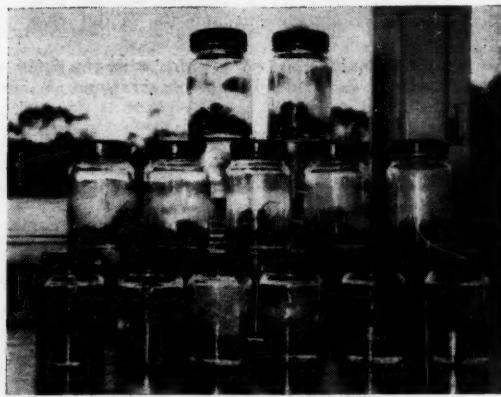


FIGURE II.

Glass jars in which *Atrax robustus* were kept in the laboratory.

The amount of venom obtained at each "milking" varied considerably. Generally, spiders which had recently arrived at the laboratory yielded more venom than those which had been in the laboratory for several months. Some spiders continued to yield well even after many months of repeated milking, whilst in others the venom yield remained consistently low. No venom was obtainable from spiders a few days prior to moulting.

TABLE I.

The Number of *Atrax robustus* Received in the Laboratory from June, 1956, to December, 1958.

Sex. ¹	Total.	Alive.	Dead.	Mortality During Transport.
Female ..	2893	2084	809	28%
Male ..	267	211	56	21%

¹ Determined by the external anatomy of the spider.

Based on the results of milking 5452 female spiders and 274 male spiders, the mean yield of venom per female spider was more than one and a half times greater than that of the male (Table II). Because the female group

TABLE II.
Venom Yields of *Atrax robustus*.

Sex. ¹	Number "Milked".	Mean Yield per Spider. (Mg.)	Standard Error of Mean. ⁴
Female ² ..	5452	0.278	<0.014
Male ³ ..	274	0.175	<0.025

¹ Determined by the external anatomy of the spider.

² Included immature and mature spiders.

³ Mature spiders only.

⁴ These figures are maximum estimates as they are based on "between-groups-variance".

also included young females and immature males (see below), the mean yield of 0.278 mg. per female spider is possibly lower than that which would have been obtained had only adult female spiders been used. On one occasion,

5.2 mg. of venom were obtained from six adult female spiders which were "milked" as soon as they had arrived at the laboratory. Thus, individual adult female spiders can yield more than 0.8 mg. of venom. The highest yield of venom obtained from individual male spiders was 0.4 mg.

A comparison was also made of the venom yield of female spiders in the different seasons (Table III). The mean venom yield during spring was significantly higher than that obtained during any of the other seasons. The differences in the mean venom yield obtained during summer, autumn and winter were not significantly different from each other.

TABLE III.
Venom Yields of Female¹ *Atrax robustus* in the Different Seasons.

Season.	Number "Milked".	Mean Yield per Spider. (Mg.)	Standard Error of Mean. ³
Spring ..	2322	0.330	<0.032
Summer ..	1267	0.237	<0.015
Autumn ..	876	0.227	<0.025
Winter ..	987	0.252	<0.017

¹ See footnotes 1 and 2 under Table II.

² See footnote 4 under Table II.

Sexual Maturity.

Adult male *A. robustus* spiders could be easily recognized by the presence of a spur on the second pair of legs, and by the modification of their palpi into intromittent sex organs.

On several occasions it was observed that a recently moulted spider amongst the group of apparent females of medium size was a male. At first it was thought that a male had been placed amongst the females by mistake. However, on subsequent occasions, examination of the cast-off skin showed no evidence of a spur or of intromittent sex organs, whilst these features were present in the recently moulted spider.

It was suspected that some of the medium-sized spiders classified as females were immature males. In order to confirm this, the internal sex organs of a series of medium-sized spiders were examined after the spider had been killed. The presence of ovaries confirmed the female status of the spider. These were absent in males, which had a coiled duct (vas deferens) and testis on each side of the abdomen.

Although spermatozoa were usually present in smears made from the internal sex organs of mature male spiders (Figure III), none could be detected in immature males.

Examination of 112 medium-sized spiders showed that 44% were males.

Length of Spider.

It was decided to determine if there were any differences in length between male and female spiders, and if such differences could be used to establish the sex of spiders. For this purpose a number of mature spiders of both sexes and medium-sized spiders which had the external features of females were used.

The length of the anaesthetized spider was measured from the blunt end of the chelicerae anteriorly to the end of the abdomen posteriorly. The spinnerets were not included. The sex of the medium-sized spiders was determined, after their length had been measured, by opening the abdomen and examining the internal sex organs.

Table IV sets out the results of these measurements in a series of mature and immature spiders of both sexes. Mature males were significantly shorter than mature female spiders. Amongst the 88 medium-sized spiders which were measured, 35 were males, but the mean lengths in the two sexes were not significantly different. Similarly, there was no significant difference in the length of

immature and mature male spiders. This suggests that, unlike females, male spiders only grow very little in length after they have attained sexual maturity. It is not known why some male spiders which measured only 22 mm. in length had fully developed external sex features, whilst others measuring up to 28 mm. in length were still immature. However, from Table I it can be calculated that if a spider measures 30 mm. or more in length, it is likely to be a female and not a male ($P = 0.05$).

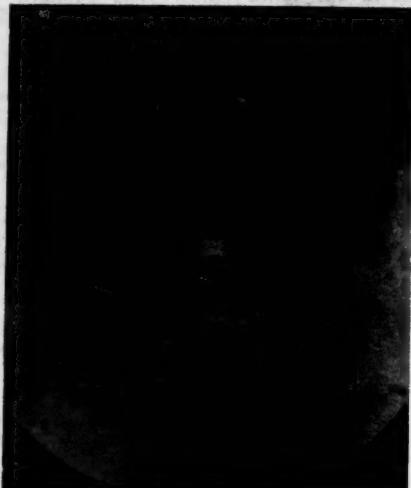


FIGURE III.
Spermatozoa of *Atrax robustus*.

Venom Content of Spiders and Toxicity of Venom.

In our earlier experiments (Wiener, 1957), which showed that male spider venom was more toxic than female spider venom and that female spiders had more venom than male spiders, we were not aware that "female" spiders could be immature males. Although the "female" spiders used in these experiments were predominantly large specimens, some medium-sized spiders were also present, and these must have included immature males.

TABLE IV.
Length of Mature and Immature *Atrax robustus* of Both Sexes.

Stage of Development.	Sex.	Number.	Mean Length. (Mm.)	Standard Error of Mean.
Mature ..	Female ..	119	24.08	0.29
	Male ..	29	25.76	0.32
Immature ..	Female ..	53	26.85	0.29
	Male ¹ ..	35	24.79	0.44

¹ Determined by examination of the internal sex organs.

It was decided, therefore, to determine the venom content and the toxicity of the venom of mature spiders of both sexes, and that of immature spiders whose sex had been ascertained, by examining their internal sex organs. Venom was extracted from the dissected venom glands, freeze dried, and its toxicity assayed in mice by the intravenous route as described previously (Wiener, 1957).

From Table V it can be seen that mature female spiders had two and a half times more venom than mature male spiders. The venom content of the venom glands of immature male and female spiders was not significantly different from each other and approximated the venom content of mature male spiders; thus, although immature spiders of both sexes which were of similar size had

comparable venom content, only female spiders continued to increase their venom as they grew older. The male spiders continued to have a lower venom content even after sexual maturity. As these differences in the venom content of spiders followed a similar pattern to that recorded earlier for the length of spiders, it appears that the venom content is directly related to the size of the spider. Since the male spider remains smaller than the female, both its venom content and its venom yield are lower.

The results of toxicity assays in mice with the different venoms (Table V) confirmed earlier observations (Wiener,

TABLE V.
Total Venom Content in Venom Glands of *Atrax robustus* and Toxicity of Venom in Mice.

Stage of Development.	Sex.	Number.	Venom Content.		Toxicity. Median Lethal Dose, Intra-venously. (Mg.)
			Mean per Spider. (Mg.)	Standard Error of Mean.	
Mature ..	Female ..	141	2.05	0.21	0.30 to 0.35
	Male ..	71	0.81	0.05	0.04 to 0.06
Immature ..	Female ..	46	1.08	0.20	0.10 to 0.45
	Male ..	35	0.92	0.12	0.35 to 0.60

1957), and showed that the venom of mature male spiders was considerably more toxic than the venom of either mature female spiders or immature male and female spiders. The lethal dose of venom from adult spiders in each sex remained fairly constant when different batches of venom were tested. However, amongst the different batches of venom obtained from immature spiders of either sex, there was a marked variation in toxicity. Contrary to expectations, the venom of immature male spiders was found to be slightly less toxic than that of immature female spiders. This indicates that male spider venom does not reach its maximal toxicity until the male spider has reached sexual maturity, whilst in the case of female spiders the toxicity of venom does not change appreciably, or decreases slightly as the spiders grow older.

Other Observations on *A. robustus*.

In order to test the validity of a common belief that the male *A. robustus* is frequently killed by the female after mating, an adult male and female spider were put together in a wide glass jar containing a layer of soil. On one occasion both spiders remained alive and well for 14 days. During this period the spiders were often found to be close together, but no mating was observed. On the fifteenth day the male spider was found to be dead. In another similar experiment the female spider was dead on the fourth day, whilst in a third experiment the male was dead on the eleventh day.

No egg sacs were ever made by *A. robustus* in the laboratory. In fact, any egg sac included when a spider was sent to the laboratory was destroyed by the spider in captivity. When egg sacs were kept separately in jars, they either became mouldy or dried up. Presumably, for proper development the eggs of *A. robustus* require maternal attention and, in captivity, conditions are unfavourable for the making of egg sacs and their maintenance by the female spider.

On one occasion an egg sac was received in which the spiderlings were ready to emerge. These have been kept in a glass jar, where each spider made a silk-lined hole for itself in the soil. The spiders were fed with live *Drosophila*, and after 12 months their average length was only 8 mm.

The moulting of a male spider was observed and assisted on one occasion. The old skin, which had split at the sides of the thorax and upper part of the abdomen, was drawn over the legs with a pair of forceps. The thorax and legs of the newly moulted spider were grey.

white in colour, which contrasted with the jet black colour of the hairs and eyes. The abdomen was dark brown in colour. After moulting, the spider was lying on its side and moved its legs continually. Three hours afterwards the gait of the spider was back to normal; when teased it stood up on its hind legs and drops of venom could be seen on its fangs. However, at this stage the spider was unable to insert its fangs into the skin of a mouse. The next day the thorax and legs had assumed a greenish-blue colour, and the fangs were red-brown in colour. The spider was able to bite a mouse, which died 20 minutes later. In the afternoon, a piece of raw meat was presented to the spider on a piece of string; the spider took it readily and sucked the juices of the meat rhythmically. Two days after moulting, the thorax was olive green in colour, and the colour of the fangs had become darker. A mouse was again bitten by the spider. During the bite the left fang broke off, and the mouse died 25 minutes later. On the sixth day after moulting, the dorsum of the thorax and the legs had assumed the chocolate-brown colour typical of *A. robustus*, but the under-surface of the thorax had a metallic bluish sheen.

There is a common belief that centipedes are amongst the natural enemies of *A. robustus*, and that they possess an immunity against the venom of this spider. In several experiments, a centipede was put together with either a male or a female *A. robustus*. Usually considerable fighting took place, and both animals bit each other—the spider offensively and the centipede defensively. The centipede appeared anxious to escape, and often protected itself by pressing its forked tail against the fangs of the spider. The results of these mutual bites varied. Sometimes neither animal succumbed; at other times either the spider or the centipede died. On one occasion, when a male funnel-web spider and a centipede had bitten each other repeatedly, the spider was dead three hours afterwards, whilst the centipede appeared unaffected. Centipedes which died did not usually survive longer than 12 to 24 hours after the bite. When the animals were left together and remained alive for several days, the spider often made for itself a compartment of silk, thereby avoiding contact with the centipede.

The inability of *A. robustus* to survive for 24 hours at an external temperature of 37° C., which has been recorded previously (Wiener, 1957), found unexpected confirmation when, during a week-end in January, the external temperature reached 40° C. Out of 280 spiders, which were stored on an outside balcony, only 10 survived.

Discussion.

Bücherl (1953) observed that the venom yield of a species of venomous spider of South America was, in general, higher in summer than in winter. However, the toxicity of the venom was similar throughout the year. He made no comparison of the toxicity of the venom of male and female spiders.

In considering the observed differences in the venom yield of male and female *A. robustus* it must be emphasized that the population of the two sexes in the laboratory was not a static one. At each "milking" different proportions of recently arrived spiders and "old" spiders were used. As eleven times more females than males were received, a greater number of freshly arrived spiders was present at each "milking" in the female group than in the male group. This may have contributed to some extent to the higher venom yield observed in the female spider and have resulted in a low estimate of the mean venom yield of male spiders.

In a series of rattlesnakes, Klauber (1956) observed that the venom yield increased with the length of the snake. He quotes a belief, expressed by Avicenna about 1000 years ago, that the poison of the male viper is more potent than that of the female. However, Klauber states that it is not known whether there are any differences beyond those resulting from the size of the snake, since the male rattlesnake eventually reaches a larger size than the female.

In the case of *A. robustus*, the female spider reaches a greater length than the male. At the same time, both the venom yield and the venom content continue to increase until the adult female spider has more than twice as much venom as the adult male spider. However, the toxicity of the venom of mature male spiders is about six times greater than the toxicity of female spider venom. On this basis the lethality of a bite by a male *A. robustus* is at least three times greater than that of the female spider. In the case of those male spiders which can yield 0.4 mg. instead of the average of 0.175 mg. of venom, an even greater lethality can be expected.

Until 1949, five cases had been recorded of death following a bite by *A. robustus* in man; in three of these the spiders were identified as males (Musgrave, 1949). In the other two cases the sex of the spider remained unknown. In June, 1958, a two-year-old girl died within a few hours after the bite of a spider in a suburb of Sydney. The spider was not seen, but the history and the circumstances of the case suggest that *A. robustus* was responsible. The seventh fatality occurred in December, 1958, when a baby, aged 17 months, died in less than one hour after being bitten twice by a funnel-web spider. The spider was identified as a male *A. robustus* (Musgrave, 1959).

Amongst the spiders forwarded by collectors, one mature male spider was received for every 11 female spiders and immature male spiders. If this ratio is a true reflection of the sex distribution of *A. robustus* in nature, it must be assumed that a bite by a mature male spider, despite its greater aggressiveness, is much rarer than that of female spiders or immature male spiders.

No adequate records are available to indicate the sex distribution amongst specimens of *A. robustus* which have caused non-fatal bites in man. However, in four out of seven fatal cases in which the spider was available for identification it turned out to be a mature male spider. It is suggested that the three other fatal cases were also caused by mature male spiders.

Observations in the laboratory support the view that the most dangerous bite is that by a mature male spider. It has been shown previously (Wiener, 1957) that the bite by this spider will almost regularly kill a mouse or guinea-pig, whilst only one out of four or five animals died after a bite by a female spider. Although the male spider has less venom than the female, the greater toxicity of its venom enabled the injection of lethal amounts of venom in nearly every animal which was bitten.

From the evidence available so far, it appears that the prognosis after a bite by an adult female spider or by an immature spider of either sex is favourable. Further information is required to confirm this view. Such information can be obtained only if the sex and length of *A. robustus* responsible for a bite are determined by external examination and, in the case of spiders less than 30 mm. long, by examination of the internal sex organs.

Summary.

The venom yield obtained by milking the female *A. robustus* was more than one and a half times greater than that of the male spider. The mean venom content in the glands of mature female and male spiders was 2.05 mg. and 0.81 mg. respectively.

There was no significant difference in the mean venom content of immature female and male spiders, which was 1.08 mg. and 0.92 mg. respectively.

Examination of the internal sex organs of spiders less than 30 mm. long, which had the external features of females, showed that 44% were immature males.

The mean body length of mature female spiders was 34.08 mm., whilst that of mature males was 25.76 mm. The venom content of female spiders increased with the length of the spider.

The toxicity of the venom of mature male spiders was about six times greater than that of mature female spiders. The toxicity of the venom of immature spiders

showed a greater variation than that observed in the case of mature spiders. The venom of immature female spiders appeared somewhat more toxic than that of immature male spiders.

The significance of these findings in relation to the seriousness of bites by *A. robustus* in man is discussed.

Acknowledgement.

I am indebted to Dr. J. J. Graydon for carrying out the statistical analysis of results obtained in this investigation.

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Reports of Cases.

AGRANULOCYTOSIS FOLLOWING THERAPY WITH PHENOTHIAZINE DERIVATIVES.

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DRUGS containing the phenothiazine nucleus generally act upon the central nervous system, either as anti-histamines preventing vomiting, facilitating hypothermia or muscular relaxation, or as depressants producing prolonged narcosis (McIlwain, 1957). A number of these drugs are in common use, and agranulocytosis has followed the administration of some, particularly promazine, chlorpromazine and mepazine (Lomas, 1954; Pisciotta *et alii*, 1958).

Agranulocytosis following the administration of phenothiazine derivatives has some characteristic features. Women are particularly affected, and mostly its onset is gradual without allergic manifestations during the second month of therapy, whether the drug is given in high or low dosage. Also readministration of the drug after recovery does not invariably produce a further granulocytopenia, which contrasts with amidopyrine-induced instances (Pollack, 1956). Usually, after an insidious onset, signs of infection appear and granulopoiesis is selectively depressed, but recovers within two weeks if the drug is ceased; in the recovery phase, examination of the peripheral blood shows initial monocytosis and later polymorphonuclear leucocytosis (Pisciotta *et alii*, 1958).

Clinical Record.

A housewife, aged 49 years, was referred to the Brisbane Hospital from a distant country centre in January, 1958. She had been treated for six weeks before her admission with "tranquillizing drugs" for mild hallucinatory depression, and had received 1250 mg. of chlorpromazine in addition to 2250 mg. of mepazine and at least 1000 mg. of promethazine at different times. Ten days before her admission she developed a sore throat and right-sided parotitis and became feverish; for this condition daily injections of procaine penicillin were given. Several days later she had ulcerative stomatitis, bilateral parotitis and continuing fever. Other antibiotics were given, but deterioration continued, and the mouth temperature rose to 105°-106° F.; auscultatory signs of pneumonia appeared, portion of the right labium majus became acutely inflamed and a profuse watery diarrhoea took the place of constipation.

On her admission to the Brisbane Hospital, the patient was obviously ill, confused and somewhat dehydrated, and had a frequent dry, unproductive cough. Her mouth temperature was 102.4° F., her respirations numbered 36 per minute and were deep, her pulse rate was 116 per minute and her arterial blood pressure was 100/60 mm. of mercury. The sclerae were slightly icteric, the liver and spleen were both tender and palpable to 3 cm. below the costal margins laterally; the fauces were very edematous and intensely reddened, and the tonsils were covered by a whitish exudate which extended patchily on to the hard palate and buccal surfaces of the cheeks, surrounding the orifices of the parotid ducts. Inspiratory crepitant rales were heard over the base of the left lung. The right labium majus and adjacent part of the mons veneris were swollen, reddened and tender to touch.

Laboratory investigations at this time showed that the haemoglobin value was 10.6 grammes per 100 ml. of blood, the erythrocytes and platelets appearing normal in stained blood smears. The total leucocytes numbered 1000 per c.mm., 3% being polymorphonuclear neutrophils, 94% lymphocytes, 1% monocytes and 2% plasma-type cells. Examination of the urine showed that the specific gravity was 1.004 and there was no appreciable albuminuria; microscopic examination of a centrifuged deposit showed seven leucocytes and one erythrocyte per high-power field, and three hyaline and two coarsely-granular casts per low power field. Stained smears of the buccal exudate showed gram-negative bacilli, numerous spores and pseudo-hyphae; *Candida albicans* and *Pseudomonas pyocyannea* were obtained on culture. Attempted cultures of two blood specimens resulted in no growth of pathogens, as did those of faeces. A radiograph of the chest showed an opaque area at the base of the left lung. On the day after her admission, when the polymorphonuclear neutrophil count in the peripheral blood was 19 per c.mm., examination of aspirated sternal marrow revealed marked depression of granulopoiesis, with a relative increase in the number of lymphocytes and plasma cells. There were no mature polymorphonuclear neutrophils, only small numbers of myelocytes and an occasional myeloblast; the red cell precursor and megakaryocyte elements appeared normal. The serum bilirubin content was 4.7 mg. and the serum alkaline phosphatase content 10.7 King-Armstrong units, both per 100 ml., and the result of the cephalin-cholesterol flocculation test was strongly positive.

Treatment was begun with intramuscular injections of crystalline penicillin, 2 megaunits every six hours, and gel-corticotrophin, 60 i.u. twice a day for the first two days, thereafter 40 i.u. twice a day. Blood cultures on the second day after her admission to hospital yielded a growth of *Ps. pyocyannea*. This organism was also isolated from the mouth, the throat and the pustules that developed in the spreading inflammation from the right labium majus. It was sensitive only to streptomycin, and the patient's fever (mouth temperature 104.5°-105.5° F.) settled within 48 to 60 hours when 1 gramme was given twice daily by intramuscular injection. However, there was not a simultaneous improvement in the general condition, which by the fourth day was considerably worse, the arterial blood pressure being 65/30 mm. of mercury. The haemoglobin value was 9.4 grammes per 100 ml. of blood. A transfusion of 500 ml. of whole blood was given, followed by 1 litre of physiological saline containing 100 mg. of hydrocortisone hemisuccinate, the blood pressure rising with the hydrocortisone infusion to 95/60 mm. of mercury. Corticotrophin injections were ceased at this time, and 300 mg. of cortisone were given daily by mouth; within 24 hours the blood pressure rose to 110/50 mm. of mercury, and was subsequently maintained at this level. However, the episode of hypotension was sufficient to reduce the urine volume to 200 ml. in the 24 hour period, and although a modified Bull-Borst régime was instituted, the blood urea level rose from normal to 184 mg. per 100 ml. within 24 to 36 hours. The jaundice deepened and the patient became progressively drowsy, the liver and spleen increasing further in size; then signs of hepatic pre-coma appeared, and the Bull-Borst régime was changed to the administration of glucose, 450 grammes per day, with tetracycline. The public

inflammation spread as an area measuring 16 by 7 cm. into the right groin and adjacent abdominal wall, and at the end of the first week most of the right labium majus was gangrenous. During this same period the buccal and pharyngeal lesions extended, some becoming gangrenous and ulcerated.

Improvement, although slight, was evident by the eighth day, and the jaundice was less. The improvement seemed to coincide with restoration of the peripheral granulocytes (see Table I), although the exact timing of

TABLE I
Summarized Haematological Reports on Peripheral Blood.

Date.	Hemo- globin. (Grammes per 100 Millilitres of Blood.)	Leucocytes.			
		Total Count per Cubic Milli- metre.	Differential Count (Percentage).		
			Poly- morpho- nuclears.	Mono- nuclears.	Myelo- cytes.
January 14	10.6	1000	3	95	0
15 ¹	9.4	650	3	97	0
16	—	650	0	96	0
17 ²	12.4	800	0	93	7
18	13.0	700	0	86	8
21 ³	13.4	10,700	75	18	7
22	13.7	15,800	76	10	7
23	10.9	13,200	89	11	<1
29	—	13,000	77	23	<1
31	11.6	16,000	84	16	<1
February 7	11.1	7800	80	19	1
18	9.8	4700	53	46	1
25	10.2	5000	65	30	5
March 3	10.9	6500	59	40	1
May 20	15.5	7000	64	36	<1

¹ Transfusion given; the platelet numbers appeared somewhat diminished on this and the next three days.

² Cortisone was administered by mouth from January 17 to February 3, inclusive.

³ Small numbers of myeloblasts, as well as early myelocytes, appeared in the peripheral blood with the increased numbers of granulocytes.

their return is not known, as unfortunately blood counts were not made on January 19 and 20. To this date one grammie of cortisone had been given; thereafter the dosage was progressively reduced, and administration ceased at the beginning of the third week. From the second week improvement was progressive; the buccal lesions, both ulcers and exudate, steadily healed, and the results of tests of liver function returned to normal, although the elevation of temperature to 100°-101° F. persisted. The gangrenous labium had separated, but the tissues beneath the associated inflammatory area were necrotic, sloughing to leave a wide subcutaneous sinus extending from the labial base to the anterior superior iliac spine; *Ps. pyocyanea* was cultured from the necrotic tissues. Treatment was conservative, and occlusion of the sinus was progressive. At the same time, radiographs of the chest showed a rounded opaque area with appearances suggesting a lung abscess in the posterior basal segment of the lower

lobe of the right lung; sputum cultures yielded a growth of coagulase-positive *Staphylococcus aureus*, *Ps. pyocyanea* and *C. albicans*. Postural drainage, with percussion and breathing exercises, was instituted.

Some ten weeks after the patient's admission to hospital, when her general condition was satisfactory, her temperature had settled and the pudendal lesion was healing adequately, the patient was discharged. The inguinal sinus was marked by a depressed scar, a linear opaque area remained in the chest radiograph at the site of the lung abscess and the results of cell counts in the peripheral blood were satisfactory. Two months after her discharge the patient remained well; the liver was palpable to 3 cm. and the spleen to 1 cm. below the costal margins, laterally, on full inspiration, and the labial base was taken up by scar tissue. The radiographic appearances in the chest were unchanged from those on her discharge from hospital; liver function tests and cell counts in the peripheral blood gave normal results. The patient has not returned for further examination.

Discussion.

The clinical history shows many of the recognized features of this type of agranulocytosis (compare Tasker, 1955; Pisciotta *et alii*, 1958); but the extent and severity of the complications were unusual, and at the outset the patient's recovery seemed unlikely. The initial symptoms developed after 4500 mg. of phenothiazine derivatives had been given over 40 days. The return of normal numbers of granulocytes in the peripheral blood around the fourteenth day is not unusual, and some authors hold that their return is almost invariable if the patient lives; in this regard, Pisciotta *et alii* (1958) suggested that steroid treatment did not manifestly improve the prognosis. In our case the relationship between steroid therapy and the granulocyte return is problematical, but cortisone appeared to relieve the circulatory collapse, of which septicaemia seemed a causal factor. *Ps. pyocyanea*, sensitive to streptomycin, was isolated from areas of localized inflammation, the blood-stream and possible metastatic sites of infection, and in view of the therapeutic response, was regarded as the causal organism. In other cases of agranulocytosis, hypotension has developed terminally for various reasons (Woodward and Solomon, 1956). The lesion causing the severe diarrhoea was not investigated beyond examination of the faeces; but colonic ulceration has been found in similar cases (Woodward and Solomon, 1956; Feldman *et alii*, 1957). Localized gangrene with sloughing, often after inflammatory changes, occurs in some severe instances of agranulocytosis; the pudendal gangrene with its extension was unusual for this type of agranulocytosis (Chirico *et alii*, 1957; Pisciotta *et alii*, 1958).

Jaundice during chlorpromazine therapy is not rare, and is mostly obstructive in type. Biochemical tests suggested that the jaundice was not obstructive in this case, but parenchymatous in nature (see Table II); a liver biopsy was not undertaken. Jaundice in comparable instances of agranulocytosis has been usually obstructive (Hodges and La Zerte, 1955), or indeterminate (Rotstein *et alii*, 1955;

TABLE II
Summarized Results of Liver Function Tests.

Date.	Serum Bilirubin Content. (Milli- grammes per 100 Millilitres.)	Cephalin- Cholesterol Flocculation at 24 Hours.	Thymol Turbidity. (Units.)	Serum Alkaline Phosphatase. (King- Armstrong Units per 100 Millilitres.)	Prothrombin Time. (Seconds.)	Serum Protein Content. (Grammes per 100 Millilitres.)								
						Patient.	Control.	Total.	Albumin.	Globulin.				
										Alpha-1.	Alpha-2.	Beta.	Gamma.	
January 15	4.7	+++	1	10.7	—	—	—	6.6	3.0	0.62	1.24	0.54	0.70	
17	—	—	—	7.1	40	16	—	6.2	2.8	0.37	0.82	1.12	1.30	
23	1.1	+++	8	6.3	18	16	—	—	—	—	—	—	—	
28	1.0	++	5	7.3	14	13	—	—	—	—	—	—	—	
31	—	—	—	—	—	—	—	—	—	—	—	—	—	
February 18	0.8	0	3	5.3	—	—	—	6.8	3.9	0.42	0.80	0.84	1.20	
21	—	0	2	4.6	—	—	—	—	5.9	3.2	0.58	0.82	0.95	—
27	0.4	0	4	5.0	—	—	—	—	5.9	3.1	0.32	0.72	0.80	0.92
May 20	0.2	0	4	6.3	—	—	—	—	5.5	2.9	0.40	0.70	0.52	0.90
								7.3	4.4	0.85	0.70	0.86	0.95	

Chiroco *et alii*, 1957). Other authors (Glaser and Adams, 1958; Pisciotta *et alii*, 1958) describe cases in which the results of flocculation tests are positive, and in at least one the serum proteins have been inverted. It has been suggested that the prognosis of phenothiazine agranulocytosis is impaired in the presence of jaundice (Schick and Virks, 1956). The phenothiazine derivatives, the septicaemia and its associated features could have contributed to the liver damage in this case.

Summary.

A history is presented of a case of agranulocytosis developing in a patient treated with the phenothiazine derivatives mepazine ("Pacatal"), chlorpromazine ("Largactil") and promethazine ("Phenergan"). *Ps. pyocyanea* septicaemia and jaundice developed, also circulatory renal failure, hepatic pre-coma and localized gangrene during the clinical course. The patient recovered, although the complications were unusually severe for phenothiazine-induced agranulocytosis.

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LINDANE POISONING IN A FAMILY.

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An unusual case of poisoning involving five members of a family of eight, resulting from accidental ingestion of lindane powder ("Gammexane" or the gamma isomer of benzene hexachloride), a well-known modern insecticide, is described.

Benzene hexachloride is a known poison; but the gamma isomer, as used commercially for insecticidal purposes, is far more toxic weight for weight, and its toxicity is increased by its solution in organic solvents. It is stored in body fat, and slowly lost through metabolism or excretion in urine, faeces or milk. Reports of serious poisoning are said to be rare; but the known effects on human beings following ingestion are principally due to stimulation of the central nervous system as manifested by *ataxia, confusion, convulsions and vomiting*. The cases described vividly confirm the cerebral intoxication attributed to the drug.

Of the five people affected, four had convulsions closely resembling epileptic fits with tonic and clonic movements and ensuing mental confusion.

A., aged 23 years, a married woman with an infant aged five months, and at the time four months pregnant, was admitted to the local hospital. Her relatives stated that after the evening meal she had played tennis for half an hour. She had then complained of sudden dizziness, had suddenly lost consciousness and had a seizure characterized by initial rigidity followed by clonic convulsions. After her recovery from this state she vomited frequently. On being examined at the hospital she was vomiting, in urgent need of using the toilet and mentally confused. As it was known that the patient was pregnant and not happily so, immediate inquiry was made as to the possibility of her having swallowed some drug in desperation. This was thought unlikely, and the patient herself, although confused and unable to think clearly, denied the suggestion. There were no signs of toxæmia of pregnancy; the blood pressure on her admission to hospital was 100/60 mm. of mercury, later rising as her condition improved to 125/80 mm. Her pulse rate was 80 per minute and the pulse was full and regular; her pupils were moderately dilated. The urine was free of albumin.

A provisional diagnosis of epileptic seizure in association with pregnancy was made, and 1.5 grains of phenobarbital were given by mouth. Twenty-four hours later she was well enough to be discharged from hospital.

The following morning the story was complicated by the fact, as told by the father, that of the remaining seven family members who had dined the previous evening, four had been stricken by vomiting and convulsions during the night. The three who had not suffered had, it was said, eaten none of the dessert or very little of it. The dessert had been prepared by one of the sisters, and consisted of a pastry base with stewed rhubarb, jelly, cream and icing sugar. The possibility of food poisoning thus became likely, and in view of the rapid onset of symptoms, staphylococcal poisoning was suspected, and an endeavour was made to collect samples of the dripping used in the pastry, and of the cream. Further information later obtained made this unnecessary, as will be seen.

Of the other victims, the earliest to become ill, was the mother (who did not seem unwell until four hours after the married daughter had been stricken), who suffered diarrhoea, but no seizure. A short while later B., aged 24 years, had a typical epileptic seizure, and on recovery from this was so confused as to attack his brother. Minutes afterwards C., aged 17 years, vomited once and promptly had a seizure. He was followed by his brother D., aged 25 years, who "fell out of bed and had a convulsion" and was violently ill an hour later. To date there have been no reported after effects in any of the victims.

It was later elicited from the father that the daughter who had prepared the dessert had sprinkled onto it what she took to be castor sugar from a glass container with a perforated top. In fact, the "castor sugar" was lindane crystal, which was purchased for use as a fly-killer to be used in an electrically worked apparatus. The lindane had apparently been transferred to the glass container and left on the kitchen table.

Summary.

A case of poisoning in five members of a family of eight, following accidental ingestion of the gamma isomer of benzene hexachloride (lindane, an insecticide), is described. The case illustrates the potent convulsive and emetic effects ascribed to the substance.

The average time between ingestion and the occurrence of symptoms of intoxication was five hours; the fact that in one victim the onset was much more rapid—about one and a half hours—may perhaps be explained by the altered rate of absorption in this subject, who was pregnant, and who had taken exercise immediately after the meal.

It is worthy of note that the amount of poison capable of inducing acute symptoms of distress in five persons was apparently not sufficient to have been tasted by them.

Reviews.

Leukemia. By William Dameshek, M.D., and Frederick Gunz, M.D., Ph.D.; 1958. New York and London: Grune and Stratton, Incorporated. 10" x 6", pp. 436, with 142 illustrations. Price: \$15.75.

THIS excellent and timely book on human leukæmia should prove most useful to both the clinician and the academic worker. It is a lucid review of the present state of knowledge of the disease, and is a worthy successor in many ways to the classical monograph of Forkner in 1938.

The authors have introduced some ideas on classification and definition of terms which are unusual and interesting. Thus, it is suggested that the term "leukosarcoma" should be revived to describe a localized neoplastic proliferation of one of the leucocytic tissues, in contradistinction to a generalized proliferation, which is leukæmia. Multiple myeloma, considered as a generalized disorder of the plasmocytic tissues, is included as chronic leukæmia. "Subleukæmia" is used as a variant of "leukæmia", and indicates a normal or low white cell count with some abnormal cells, while "leukæmia" is reserved for the state in which no abnormal cells can be seen in the peripheral blood. It is doubtful whether this additional term serves any very useful purpose.

It is difficult also to agree with the authors, in their conclusion about the prevalence of the disease, that "there is as yet no decisive evidence to prove an actual as opposed to an apparent rise in incidence".

The chapter on the pathology of the leukæmia cell describes modern methods of examination, including biochemical changes, staining methods and electron microscope studies.

Instead of the usual custom of describing clinical manifestations under type headings, signs and symptoms common to all types are presented first, and this serves to emphasize the many similar features in all varieties.

The "myeloproliferative" disorders are described in some detail, and include polycythaemia and the Di Guglielmo syndrome. The close relationship between these disorders and leukæmia is illustrated by some case reports.

The book concludes with a review of present-day methods of treatment and the indications for using the various drugs now available.

Physical Diagnosis: The History and Examination of the Patient. By John A. Prior, M.D., and Jack S. Silberstein, M.D.; 1958. St. Louis: The C. V. Mosby Company, Melbourne: W. Ramsay (Surgical) Limited. 9" x 6", pp. 388, with 193 illustrations. Price: £4 2s. 6d.

In the introduction, the authors emphasize that their objective in writing this book was to stress the painstaking art of history taking and to present methods for examination of the various bodily systems, as carried out at the Ohio State University College of Medicine.

Details of physical examination are not confined to the cardio-vascular, respiratory, alimentary, nervous and motor skeletal systems. Included are chapters on examination of the breast, the male and female genitalia, the eyes, ears, nose and throat and the extremities. There is also a useful section on paediatric examination.

That a book of this type should have eight contributors apart from the two authors is indicative of the growth of specialized medicine. However, the virtue of specialized knowledge is lessened by the different styles and approaches of the individual contributors. The illustrations and drawings are generally satisfactory, and references to relative literature are given at the end of each section.

The book can be recommended to medical students as being generally satisfactory as an introduction to history taking and the elucidation of physical signs. It is obviously intended for undergraduates. The type is clear and reading is easy and straightforward. It is a pity that the book is so costly.

Pain. By Harold G. Wolff, M.D., and Stewart Wolf, M.D.; Second edition; 1959. Oxford: Blackwell Scientific Publications. 8½" x 5½", pp. 134, with 20 illustrations. Price: 32s. 6d. (Abroad).

THE authors have compiled a pleasant and informative little book on the many aspects of pain as it affects the patient. There is much in it to remind the practising physician of basic principles and associated factors in the

study of pain, which may well be overlooked in the high-speed rush of modern existence.

The first chapter is concerned mainly with the stimuli producing pain, and the paths in the nervous system—both central and peripheral—in which it travels to reach consciousness and produce associated phenomena, such as hyperalgesia, emotional accompaniments, etc. A clear distinction is drawn between two highly important yet little realized factors—the threshold of pain perception, which is a relatively constant factor, and the individual's reaction to pain, which is extremely variable. Their apparatus to produce pain and methods of measurement make interesting reading.

The second chapter is concerned with pain originating in various bodily structures and organs, and attempts are made to locate the source of pain in some of the lesser understood regions; of the latter, most attention is directed towards the head and neck areas, and there is much comment on headache.

A final chapter on diagnosis and management reminds the reader of the variable qualities of pain encountered on the daily round, whilst treatment is discussed largely in general terms, with emphasis on conservative measures. A brief résumé of surgical methods completes the discussion. Humane comments on the care of the dying and the family in attendance complete the book.

Babies Without Tears: A Mother's Experiences of the Lamaze Method of Painless Childbirth. By Marjorie Karmel; 1959. London: Secker & Warburg. 7½" x 4¾", pp. 208. Price: 15s. 6d. (English).

THE Lamaze method of "accouchement sans douleurs" is described by Marjorie Karmel in this book. It is written in the light of her personal experiences of two pregnancies and confinements. She had her first baby in Paris, where she was instructed by Dr. Fernand Lamaze, who has adopted certain psychological and neurological theories of Pavlov and claims to be able to ensure childbirth without pain. The instruction included prolonged and detailed preparation by a physiotherapist trained in the method. The second confinement in New York followed an induction of election aided by oxytocics, and appears to have been entirely normal.

It is difficult to distinguish a clear-cut difference between this method and those based on the teaching of Grantly Dick Read. The Lamaze method agrees with the principle of conquering fear by knowledge and, in addition, makes use of conscious mental and physical control of the birth process.

The first two parts of the book are the patient's experiences and opinions—of confinements, doctors and hospitals. The appendix contains a brief summary of the method, an awareness of which would be of value to those in obstetrical practice, if only to avoid the criticisms made by the author. There is a list of references for the enthusiast in psychosomatic obstetrics. However, it is thought that the main appeal will be to the patients themselves, the women who want their babies, if possible, without tears.

Clinical Obstetrics and Gynaecology. Volume I, Number 4; December, 1958. "Symposium on Operative Obstetrics", edited by J. Robert Willson, M.D.; "Symposium on Genital Cancer", edited by Daniel G. Morton, M.D. New York: Paul B. Hoeber, Incorporated. 9¾" x 6¾", pp. 281, with illustrations. Price: \$18.00 per year (four issues).

The fourth quarterly number of "Clinical Obstetrics and Gynaecology" maintains the high standard of its predecessors.

In a foreword, J. Robert Willson, the guest editor of the symposium on operative obstetrics, advocates a wider practice of consultation, and the channelling of difficult procedures into the hands of those most capable of performing them. Tommy Evans covers well the gamut of cervical and uterine injuries. He inclines to the radical belief of "once a Caesar, always a Caesar", and shows little enthusiasm for repair of the ruptured uterus. There are some imaginative diagrams (one representing a uterine inversion caused by cord traction), which are out of place in a scientific treatise. Goethals summarizes the indications for various methods of breech delivery, favouring elective total extraction under ether and oxygen anaesthesia for the full-term foetus. Savage writes a comprehensive account of forceps delivery, and Cosgrove the chapter on Cesarean section, analysing nearly 2000 cases from the Margaret Hague Hospital. Holly writes briefly

and to the point on version. Barter describes the repair of the incompetent cervix to prevent mid-trimester rupture of membranes. Russell discusses the problem of termination of pregnancy and sterilization in all its aspects. There are informative chapters on dystocia due to large fetus, perineal and vaginal injuries, and anesthesia.

Daniel Morton is the guest editor of the second symposium on genital cancer. He stresses that the responsibility of achieving better results in the over-all problem of malignant disease lies with every physician—early diagnosis is essential. Concerning the treatment of Stage 0 carcinoma of the cervix, he quotes several series of cases in which conization has been followed by repeated cytological examinations. Recurrence does take place, but is rare. For the young woman this course is indicated; for the older woman past child-bearing, total hysterectomy (or local irradiation) is preferable. Traut writes on early diagnosis, emphasizing the value of cytological examination in growths of the cervix, corpus and tube. Herbert Schmitz and Smith of Chicago summarize radiation treatment of carcinoma of the cervix. This excellent paper includes a discussion of basic principles, the Schmitz staging of cervical cancer, treatment (with special reference to cancer and pregnancy), follow-up investigation and results. Joe V. Meigs contributes his classical and well-illustrated description of the radical operation for cervical cancer, with comments arising out of his long experience and thought on the subject. Brunschwig surveys the value of radical surgery for recurrent cancer in the various pelvic organs. Randall stresses the importance of pre-operative irradiation for carcinoma of the endometrium, especially when the histological findings suggest a fast-growing anaplastic type. Surgery is not enough. The modified Wertheim procedure is the operation of choice, gland excision being considered of more prognostic than therapeutic value. Howard Taylor contributes a long and interesting paper on cancer of the ovary. McKelvey describes his operation for vulval cancer using local anaesthesia. His results are very good. Te Linde and Brack analyse the results of treatment at Johns Hopkins Hospital in a small series of cases of cancer of the vagina, and there is an account from New Orleans of 17 cases of cancer of the Fallopian tube. Houston Everett writes an excellent survey of renal and intestinal complications of cancer treatment, both surgical and radiotherapeutic.

As in previous reviews, this quarterly series is highly recommended.

Clinical Neurophysiology. By John Marshall, M.D., F.R.C.P. (Ed.), M.R.C.P., D.P.M. (Lond.); 1959. Oxford: Blackwell Scientific Publications. 8 $\frac{1}{2}$ " x 5 $\frac{1}{2}$ ", pp. 304, with 157 illustrations. Price: 37s. 6d. (Abroad).

UNTIL quite recently, texts on the physiological basis of clinical neurology have been written almost exclusively in terms of applied neuroanatomy. Very little of this traditional approach is presented in John Marshall's "Clinical Neurophysiology", which is written almost exclusively from the standpoint of experimental neurophysiology. In view of the fact that the author is a clinical neurologist, it is rather surprising to find the emphasis so strongly on the laboratory rather than the clinic. It is the author's professed aim "to present such scientific knowledge about the nervous system as seems relevant to the clinical scene . . . and to give the clinician a sufficient background of knowledge to enable him to view his clinical practice from a scientific standpoint and appreciate the significance of the advances in neurophysiology which are being made".

The first chapter deals with the nerve impulse, and succeeding chapters discuss peripheral nerve and muscle, synaptic transmission, the spinal cord, the brain-stem and so on up to the cerebral cortex. The first third of the book contains a particularly good account of the great strides that have been made in recent years in our understanding of the fundamental nature of nervous conduction. Such an account is particularly welcome because, up to the present, this new knowledge has to a large extent been available only in the original papers or specialist reviews. As a basis for neuropharmacology, this work is likely to be of increasing importance for the clinical neurologist. However, as Dr. Marshall's account ascends the neuraxis, it becomes increasingly sketchy, perhaps reflecting decreasing knowledge or fewer advances of significance for the clinical scene. The final two chapters on the auditory and visual systems are scarcely sufficiently detailed for a not-very-comprehensive text-book of physiology.

In general, however, the book is a valuable addition to the increasing number of smaller monographs concerned

with the physiological basis of clinical medicine, largely because it brings together and summarizes a neurophysiological literature not readily available to the clinician. It is clearly written and singularly free of specialist jargon; but the author seems often to be addressing himself to the undergraduate rather than to the post-graduate reader for whom the book is primarily intended. It could certainly be read with profit by the undergraduate student.

Die pränatale Infektionen des Menschen: Unter besonderer Berücksichtigung von Pathogenese und Immunologie. By Dr. Heinz Flamm, with a foreword by Professor Dr. Richard Bieling; 1959. Stuttgart: Georg Thieme Verlag. 9 $\frac{1}{2}$ " x 6", pp. 150. Price: DM 19.80.

THIS monograph is a concise and comprehensive review of all the infectious diseases in the widest sense of this word which a mother may transmit to her unborn baby. It begins with an account of maternal rubella and its consequences; a discussion of poliomyelitis follows, and here both aspects—the influence of pregnancy on the course of poliomyelitis in the mother, as well as the influence of maternal poliomyelitis on the fetus—are fully treated. Infections with other neurotropic viruses are then listed. A useful account of cytomegalic inclusion disease is given, and the chapter ends with brief references to the effect on the fetus of practically all other known virus diseases.

The next section deals with the infections by bacteria and fungi. Infections by staphylococci and streptococci are dealt with first; then the discussion extends to tuberculosis, syphilis and listeriosis. This section ends again with a brief account of all the other bacteria that may occasionally be transmitted to the fetus.

A section on infections by animal parasites follows, malaria and toxoplasmosis are especially considered, and there is even a chapter on worm infestation of the fetus.

The book ends with a discussion of the immunological aspects of the prenatal and neonatal period, special attention being given to the problem of passive and active immunization of the fetus and newborn.

This vast field is covered in about 100 pages, while the following 30 pages are entirely devoted to a most valuable list of references. It is this section that will be of the greatest benefit to the reader who cannot follow the German text throughout the book. The list contains a very large number of titles of modern papers in the English language, and includes comprehensive review articles in English as well as in German. Any paediatrician or pathologist concerned with the perinatal period will find this book most interesting.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Neuropharmacology: Transactions of the Fourth Conference, September 25, 26 and 27, 1957, Princeton, N.J.", Edited by Harold A. Abramson, M.D.; 1959. New York: Josiah Macy, Jr., Foundation. 9 $\frac{1}{2}$ " x 5 $\frac{1}{2}$ ", pp. 286, with 48 illustrations. Price: \$5.00.

Contains articles and discussions on the effect of respiratory poisons and anoxia on Siamese fighting fish in relation to LSD-25 reaction, on clinical studies with tarazine, on "stop" and "start" systems and on some relations between chemical structure and physiological action of mescaline and related compounds.

"Comparative Endocrinology", edited by Aubrey Gorbman; 1959. New York: John Wiley & Sons, Incorporated. London: Chapman & Hall, Limited. 9 $\frac{1}{2}$ " x 5 $\frac{1}{2}$ ", pp. 768, with many illustrations. Price: \$15.00.

Proceedings of the Columbia University Symposium on Comparative Endocrinology, held at Cold Spring Harbor, New York, May 25 to 29, 1958.

"Physiology of Cardiac Surgery: Hypothermia, Extracorporeal Circulation and Extracorporeal Cooling", by Frank Gollan, M.D.; 1959. Springfield, Illinois and U.S.A.: Charles C. Thomas, Publishers. Oxford: Blackwell Scientific Publications. 8 $\frac{1}{2}$ " x 5 $\frac{1}{2}$ ", pp. 108, with 18 illustrations. Price: 34s. (English).

The Beaumont Lecture, Wayne County Medical Society.

The Medical Journal of Australia

SATURDAY, NOVEMBER 7, 1959.

PEPTIC ULCER: EVIDENCE AND ARGUMENT.

SIR HAROLD HIMSWORTH, in his capacity as secretary of the Medical Research Council of Great Britain, has pointed out with respect to peptic ulcer that the high prevalence of the disease, its claim on hospital beds and its unsolved aetiology make it worthy of further intensive study. It is instructive therefore to consider some of the salient facts and conjectures put forward on the subject up to date. It has been accepted that peptic ulcer results from an imbalance between the digestive action of pepsin in an acid medium and the natural resistance of the mucosa, the so-called ulcer equation (W. I. Card¹). Although both gastric and duodenal ulcer have certain morbid features in common, in recent years it has been customary to distinguish between them on aetiological as well as on clinical grounds. It seems accepted also that both constitutional and environmental factors are involved in aetiology, and the distinction between gastric and duodenal ulcer gained support from the family studies of R. Doll and T. D. Kellock² who showed that the fathers and male siblings of duodenal ulcer subjects had a higher incidence of peptic ulcer than could be expected by chance, and that most of the ulcers were duodenal. Contrariwise, fathers and male siblings of gastric ulcer subjects suffered from an excess incidence of gastric ulcer. The gastric secretory pattern differs between the two diseases, hypersecretion being present in association with duodenal ulcer, but not with gastric ulcer. Epidemiological studies support the distinction, for since the first decade of this century, gastric ulcer has shown a rapid decline in incidence in females, while duodenal ulcer has become increasingly prevalent in both sexes, changes which cannot be attributed to improved methods of diagnosis. Although duodenal ulcer is the more common form of the disease in countries of European culture and has attracted more attention, it is well recognized that gastric ulcer has a much higher mortality rate in relation to morbidity at all ages.

In view of all this it is interesting to turn to recent evidence produced by I. N. Marks and H. Shay of Philadelphia,³ which they interpret as showing that there may be little difference in the mechanism of patho-

genesis between gastric and duodenal ulcer, irrespective of the broad aetiological considerations. They take as their starting point cases of combined gastric and duodenal ulcer and compare them with cases of gastric ulcer alone and duodenal ulcer alone, as regards gastric histological features and gastric secretory capacity, using the augmented histamine test. Combined ulcer shows a secretory pattern intermediate between the hypersecretion of duodenal ulcer and the normal secretory capacity of gastric ulcer, and this confirms the previous data of Card and others of Edinburgh.⁴ Single ulcers located in the immediate prepyloric region also show the same secretory capacity as combined ulcer. Marks and Shay point out that most gastric ulcers are located on the lesser curvature, not in the acid- and pepsin-secreting mucosa, but in prepyloric mucosa and its projections along the lesser curvature, and they show that many ulcers situated above the radiological angulus or incisura actually occur in prepyloric mucosa. This confirms recent independent observations along the same lines from Japan,⁵ which appears at the present time to be the country with the highest incidence and mortality from gastric ulcer. When chronic gastric ulceration is present, a spreading zonal gastritis extends into the secretory mucosa of the fundus leading to a diminution in gastric secretory capacity. Duodenal ulcers require a high secretory capacity for their production; pyloric gastritis is a frequent accompaniment, leading to reduced mucosal resistance and an imbalance in the ulcer equation with resulting secondary gastric ulceration. Gastric ulcer then leads to secretory depression by producing a spreading gastritis. This sequence suggests that there is little difference in the essential pathogenesis between gastric and duodenal ulcer.

If this were true, it would be difficult to decide whether duodenal or the immediate prepyloric mucosa had the greater natural resistance, for if it takes hypersecretion to produce duodenal ulceration alone, greater resistance in the prepyloric mucosa would be implied; so that prepyloric ulcer alone should be accompanied by a greater secretory capacity still, or it should be invariably accompanied by duodenal ulcer, neither of which is true. That gastric hypersecretion precedes duodenal ulcer and is not an effect has been recently demonstrated on United States Army inductees by Mirsky,⁶ using serum pepsinogen estimations. Men who on induction yielded negative findings from a barium meal examination done as part of the study, and who later developed a radiologically proven duodenal ulcer, all came from the group who had high serum pepsinogen levels at the time of induction.

Both Marks and Shay and M. Andreassen and his colleagues of Copenhagen⁷ draw attention to the association between gastric and duodenal ulcer in the same patient. There is little doubt that the frequency of the association is underestimated in most statistics on peptic ulcer and is much higher than can be expected by chance. Andreassen demonstrates that in cases of combined ulcer, duodenal ulcer precedes the gastric ulcer in a large

¹ In "Modern Trends in Gastroenterology", 1952, Butterworth, London: 380.

² *Ann. Eugen. (Lond.)*, 1951, 16: 231.

³ *Lancet*, 1959, 1: 1107 (May 30).

⁴ *J. roy. Coll. Surg. Edin.*, 1959, 4: 85 (January).

⁵ *Gastroenterology*, 1959, 36: 45 (January).

⁶ *Amer. J. dig. Dis. (N.S.)*, 1958, 3: 285 (April).

⁷ *Lancet*, 1959, 1: 1111 (May 30).

proportion of the cases; and both the Danish and Philadelphia groups suggest that the gastric ulcer is secondary to gastritis associated with duodenal ulcer. Neither group of workers, nor R. Mangold of London,⁸ finds support for the previous hypothesis of H. D. Johnson⁹ that the association and sequence result from gastric stasis as a complication of duodenal ulcer. Balanced against these arguments one must take into account the differing age distribution and relative frequencies of gastric and duodenal ulcer taken separately. The attack rate of duodenal ulcer does not increase with age after 30 years,¹⁰ but the incidence of gastric ulcer increases progressively.¹¹ Mangold has demonstrated that the age distribution of combined gastric and duodenal ulcer is very similar to that of gastric ulcer alone, and therefore the age of onset of gastric ulcer does not appear to be influenced by the presence or absence of a duodenal ulcer. If we bear age differences in mind, it can be anticipated that in cases of combined ulcer, the duodenal ulcer would have occurred first by chance eight times out of ten, and there is therefore no necessity for postulating a special pathological mechanism to explain the sequence.

No studies of this kind, or the arguments based on the results, can be expected to explain all the observed phenomena, but their importance lies in producing new hypotheses which can be tested, a process by which both knowledge and understanding advance. The previously mentioned epidemiological data point to changing environmental factors in the aetiology as opposed to the pathogenesis of peptic ulcer, and complementary studies in this direction are required if mortality and morbidity from peptic ulcer disease are to be reduced.

Current Comment.

INAPPARENT PYELONEPHRITIS.

PYELONEPHRITIS, whether acute or chronic, has probably never been regarded as a trivial complaint, but the introduction of the sulphonamide drugs in 1938 appeared for a time to have enormously simplified the treatment in the great majority of cases. However, there still lurked in the background the shadow of doubt as to the ultimate prognosis in an unspecified proportion of patients. The availability of effective antibiotic agents soon emphasized the problem of the patient with recurrent pyuria, a question which has of late received much attention from paediatric physicians and surgeons. Recently, there has been increasing realization of the fact that the absence of pyuria is no proof of the absence of infection. A significant degree of bacteriuria may exist in the absence of leucocytes in the urine, and in the absence of such symptoms as dysuria, increased frequency and nocturia. What is the true significance of such a finding? In a recent paper J. P. Sandford¹ discusses inapparent pyelonephritis as an intermediate and occult stage which may occur between the original acute attack (often in childhood) and late chronic pyelonephritis, which often ends in hypertension and uræmia. He points out that the presence of pyelonephritis

is not infrequently disclosed at autopsy in cases in which the disease was unsuspected during life. Various investigators have found the presence of pyelonephritis in from 6% to 20% of autopsies performed, yet the diagnosis of pyelonephritis was made during life in only about one-fifth of these cases. Sandford states that so-called pyelitis of infancy has usually been considered a self-limiting disease, but that long-term evaluation has failed to justify such optimism. In follow-up studies most patients were asymptomatic, yet in many cases there was evidence of persistent renal disease, such as abnormal findings in excretory pyelograms, persistent pyuria, or the presence of bacteria in cultures of urine. Sandford then discusses the methods of recognizing this phase of apparent inactivity. Evaluation of asymptomatic bacteriuria depends on the differentiation of actual infection from contamination during collection of specimens for culture. The urethra normally contains bacteria in its distal 2 to 3 cm. Hence the most meticulous cleansing technique cannot avoid contamination with these organisms, either in voided or in catheter specimens. Emphasis has recently been placed on techniques utilizing estimation of the number of bacteria per millilitre of urine to facilitate differentiation between "significant bacteriuria" and contamination. Consensus of opinion places the number which distinguishes significant bacteriuria from contamination in the range between 10,000 and 100,000 bacteria per millilitre of urine. Most specimens contaminated during collection contain less than 1000 bacteria per millilitre; when acute pyelonephritis is present, the specimens show a bacteriuria of more than 100,000 per millilitre. It was found by H. Kass² that only 1% of patients had bacterial counts in the range between 10,000 and 100,000 per millilitre, and that when these counts were repeated with the use of a first morning specimen of urine, the distinction between contamination and bacteriuria was readily made. R. A. MacDonald and his colleagues³ studied the relationship of bacteriuria to pathological lesions in the urinary tract in a series of 100 unselected autopsies on adults; they found that the existence of a true bacteriuria (over 100,000 per millilitre) showed a good correlation with the presence of pyelonephritis, and they suggest that such a relationship may also occur during life. Sandford points out that an association between chronic pyelonephritis and arterial hypertension was demonstrated as long ago as 1939, and remarks that this association is very suggestive, though a definite causal relationship has not been proved. Another indication of the potential danger of asymptomatic bacteriuria is Kass's finding that about 40% of women who have this condition during pregnancy will develop an acute infection if not given antimicrobial agents. Sandford concludes his paper by stating that many important questions still await study and elucidation. He asks: Are patients with inapparent pyelonephritis predisposed to subsequent acute apparent infections? Does inapparent pyelonephritis progress to subsequent chronic pyelonephritis with hypertension and renal insufficiency? Does therapy alter the course of inapparent pyelonephritis?

SEROTONIN.

THE presence of a vasopressor factor in blood has been known for a very long time. It was isolated by Rapport in 1948, called serotonin and shown to be 5-hydroxytryptamine, a derivative of tryptophane. A vast amount of research has been done on serotonin in the past few years, but still there is no clear indication as to what its function is in the human body. An extensive review of more recent findings has been given by A. Sjoerdsma,⁴ who himself has done a great deal of the research. Normally, blood contains about 0.1 to 0.2 µg. per ml., practically all of which is in the blood platelets. About

¹ Brit. med. J., 1958, 2: 1193 (December 13).

² Lancet, 1957, 2: 518.

³ Medical Research Council, Special Report Series; 1951, H.M. Stationery Office, London: 276.

⁴ Schweiz. Z. allg. Path., 1958, 21: 405.

⁵ J. Amer. med. Ass., 1959, 169: 1711 (April 11).

⁶ A.M.A. Arch. intern. Med., 1957, 100: 709 (November).

⁷ New Engl. J. Med., 1957, 256: 915 (May 16).

⁸ New Engl. J. Med., 1959, 26: 181 and 231 (July 23 and July 30).

90% to 95% of the serotonin in the human body is in the gastro-intestinal mucosa, but smaller amounts occur in the spleen and brain. Of particular interest is the fact that in malignant carcinoidosis, caused by malignant carcinoid tumours (argentaffinomas), large quantities of serotonin are found in the tumour cells and there is a considerable increase in the blood content of serotonin. A useful discussion on the metabolic pathway of tryptophane to serotonin has been given by R. M. Donaldson and S. J. Gray.² Tryptophane is oxidized to 5-hydroxytryptophane, and this, by loss of carbon dioxide, is converted into 5-hydroxytryptamine (serotonin). Only a small part of the tryptophane ingested follows this metabolic pathway. Most of the serotonin in the body is oxidized and deaminated to 5-hydroxyindolacetic acid (5-HIAA) and excreted in the urine. The determination of this substance in the urine gives the best indication of the production of serotonin in the body and is used to aid in the diagnosis of malignant carcinoidosis, for in this condition there is a great increase in the amount of 5-HIAA in the urine. Urinary 5-HIAA, however, normally represents to a large extent serotonin produced in the intestinal tract. The entire circulating blood contains at most 1 mg. of serotonin, and if the whole of this was excreted as 5-HIAA in a day, the total excretion would still fall within the range of normal daily variation in most subjects. Under normal conditions the whole of the serotonin in the blood appears to be in the blood platelets, and these merely absorb serotonin in some manner, for there is no evidence that platelets can synthesize or degrade serotonin. No role has been found for serotonin in platelet function or haemostasis. The finding of serotonin in the brain has occasioned much research. It appears that serotonin produced peripherally does not enter the brain, but serotonin can be synthesized from its precursor, 5-hydroxytryptophane, by cerebral tissue. Serotonin is not equally distributed in the brain, most being found where automatic integration occurs. It is believed by many, on evidence largely circumstantial, that serotonin is of physiological importance in brain function, but its role is still unknown. It is known that certain psychotropic drugs such as reserpine, iproniazid and some substituted hydrazines, which act as monamine oxidase inhibitors, interfere with serotonin metabolism in the brain and produce symptoms related to the brain. Thus reserpine liberates serotonin and has a depressant effect on the brain, iproniazid blocks serotonin degradation and has a stimulating effect.

The clinical features of the carcinoid syndrome should give some clues to the physiological functions of serotonin. These include episodic flushing of the skin, patchy cyanosis, telangiectasia, pellagra-like skin lesions, bronchoconstriction, oedema, atypical valvular heart lesions, abdominal cramps and diarrhoea. So far very little has come out of studies on carcinoidosis. There is some evidence that serotonin may have something to do with allergic manifestations, but different animals react in different ways.

Serotonin is present in nettle stings, wasp venom, scorpion venom and "itch" powder, so may be involved in the cutaneous reactions associated with these substances. Serotonin has been found in minute amounts in several foodstuffs, but only in bananas so far have important amounts been detected. J. A. Anderson, M. R. Ziegler and D. Doeden³ found that feeding with bananas increased the excretion of 5-hydroxyindol acetic acid in the urine. They found that an average banana contains about 4 mg. of serotonin. J. Crout and A. Sjoerdsma⁴ studied the significance of serotonin and other amines in bananas. From their studies, it is evident that ingestion of bananas may increase 5-HIAA excretion enough to influence seriously any research study in which this compound is measured, and even to suggest falsely a diagnosis of malignant carcinoid. They also found that bananas contain significant amounts of dopamine (3,4-dihydroxyphenylethylamine) and 1-noradrenaline, amounts

sufficient to interfere with urinary excretion of these substances in such conditions as phaeochromocytoma. None of these substances are present in bananas in amounts sufficient to cause symptoms in the person eating the bananas unless an abnormal number are eaten.

The present position regarding serotonin is that we have a very interesting substance, potentially of importance metabolically, but so far there are no clear indications as to its function in the body.

INBREEDING IN SWEDEN.

ISOLATION has been studied carefully by many biologists; for example, according to Charles Darwin the isolation of the Galapagos Islands led to the production of many new species there. Many human epidemiologists have also realized the importance of the size of human population aggregates for the spread of human disease, and the geneticists of Scandinavia have carried out many investigations on recessive characters. These are most commonly detected in consanguineous marriages, which are often commoner in small isolated communities. In his treatise on first-cousin marriages in Sweden C. H. Alström (1958)⁵ is following on the work of Sewell Wright and Gunnar Dahlberg, who attempted to measure the size of the "genetic isolate" in different areas. This term is meant to make more precise the idea that the people of say, Sweden, do not mate at random, but are more likely to marry persons who live near by. However, the population is broken up not only by geographical but also by social factors. The Jewish population of pre-war Germany is a well-known example, and many recessive defects were detected in it because religious isolation led to increased inbreeding. The Swedish noble families also act as isolates. Alström points out that the first-cousin marriage rate was 3.5% in 1750-1759 in the Swedish nobility, about ten times as high as in the general Swedish population. The old canon law forbade such marriages, but in the period 1680 to 1844 the King in Council could give dispensation. Now there is no prohibition.

Alström has reviewed the whole problem of "isolation" in Sweden as measured by consanguineous marriages. An example of isolation by social factors is provided by the Swedish nobility. The high nobility is more inbred than the low nobility, because of its smaller size and its smaller connexion with the not-noble population. Further, the low nobility has been recruited especially in the years 1650 to 1750 from the not-noble population, although only 10% of houses have been recruited since 1800. In the general Swedish population a high frequency of first-cousin marriages is found in the sparsely settled forested regions of the north, and Alström concludes that distance is the chief isolating factor in Sweden. The reasons for this survey are to ascertain the genetic background of schizophrenia and manic-depressive psychosis in the country of Östergötland and to study the genetic dynamics of the whole country. Alström discusses some limitations of the methods. In human populations there is certainly not "random" mating, and the relations between the size of the isolate and the degree of inbreeding are not easy to assess. In practice, since brother-sister and nephew-aunt marriages are forbidden and distant relationships hard to trace, only first-cousin marriages are of importance. The proportion of such marriages has been practically constant in Sweden for the last hundred years.

Human genetics will surely become an important branch of medical theory and practice in the future. At present, there are few medical fields in which genetic theory is sufficiently well developed to be of value to clinicians, but painstaking studies like Alström's will add to the knowledge necessary for some synthesis in the future.

² A.M.A. Arch. intern. Med., 1959, 104: 330 (August).

³ Science, 1958, 127: 236.

⁴ New Engl. J. Med., 1959, 26: 23 (July 2).

⁵ "First Cousin Marriages in Sweden 1750-1844 and a Study of the Population Movements in Some Swedish Subpopulations from the Genetic-Statistical Viewpoint", Acta genet. (Basel), 8: 295.

Abstracts from Medical Literature.

MEDICINE.

Anticoagulation Therapy in Acute Myocardial Infarction.

F. J. CONRAD AND N. O. ROTHERMICK (*A.M.A. Arch. intern. Med.*, March, 1959) present an analysis and review of a clinicopathological study of 623 patients with acute myocardial infarction and the role of anticoagulation therapy in their management. The patients were seen at the Ohio State University Hospital during the sixteen-year period from 1942 to 1957. Of these patients, 146 received adequate anticoagulation therapy, 369 did not receive adequate anticoagulants and 108 received anticoagulants but did not fulfil the criteria established for adequate anticoagulation therapy. A total of 248 patients (39%) died, and autopsies were obtained in 147 cases. The study showed that three times as many of the patients not receiving anticoagulation therapy died as in the group receiving such therapy. Also, there were three times as many thrombo-embolic complications in the group not receiving anticoagulants as in the group receiving anticoagulants. Even though the mortality and morbidity in the good risk patients are much less than in poor-risk patients, the good-risk patients receiving anticoagulation therapy had only one-sixth of the mortality and one-half of the morbidity of the good-risk patients not receiving such therapy. The danger associated with the use of anticoagulants is negligible compared to the preventive mortality and morbidity. Hence it is advised that all patients with acute myocardial infarction should receive anticoagulation therapy and that anticoagulants should be started immediately.

Transfusion Reactions.

G. M. BARLAS AND W. J. KOLFF (*J. Amer. med. Ass.*, April 25, 1959) discuss transfusion reactions due to the transfusion of incompatible blood and their treatment, especially with the artificial kidney. The authors have treated 16 patients with such reactions between 1954 and 1958 in the Department of Artificial Organs, The Cleveland Clinic Foundation. Twelve seriously ill patients were treated with dialysis, and three of these died. The other four patients recovered without dialysis. These 16 patients were transferred for treatment from other hospitals, three from large hospitals and 13 from small hospitals. In the small hospitals, the accidents often resulted from mismatching, but the three cases in large hospitals were the results of clerical errors. The authors comment that these figures do not mean that transfusion reactions occur less frequently in large hospitals, but only that fewer patients were transferred from large hospitals. Details are given in 13 cases. The authors state that there are three phases in such reactions. These are: the acute reaction phase, the oliguric phase and the diuretic phase. The acute reaction phase is characterized by chill, fever, lumbar pain, flushing or cyanosis,

headache, nausea, rapid shallow breathing and distension of neck veins. There may be hypotension, tachycardia or collapse. Haemoglobinuria occurs, and jaundice follows in three to 24 hours. Haemoglobinuria occurs in the first 24 hours, after which it disappears and is followed by urinary suppression and uremia (the oliguric phase). In this, peripheral and pulmonary oedema and hypertension occur. Convulsions, mental changes, drowsiness, psychosis or stupor may follow. Sudden death with or without potassium intoxication occurs in some cases. A diuretic phase may follow. Treatment includes cross-matching the patient's blood with blood from the incriminated bottle. If the diagnosis is established, a solution of 5% dextrose in water (two litres) should be given intravenously at once, to prevent blocking of the kidney tubules with acid haem. In the oliguric phase water is given by mouth if possible, up to 500 ml. daily. It may be necessary to administer hypertonic dextrose solution intravenously. Mannitol given at once intravenously, in a dose of 50 to 100 ml. of a 25% solution, may increase urinary flow by osmotic diuresis. If hypertension, pulmonary oedema or convulsions occur, venesection should be done, removing 300 to 500 ml. of blood. To remove oedema fluid, sodium sulphate (45 grammes) in warm water given by mouth may induce diarrhoea. It is considered of doubtful value. Ultrafiltration with the artificial kidney is the most effective way to remove oedema fluid. Hyperpotassium in the oliguric phase is best detected by determining the serum potassium content with the flame photometer.

Poliomyelitis Prevention.

J. E. SALK (*J. Amer. med. Ass.*, April 18, 1959) discusses poliomyelitis vaccine preparation and administration. This has now been observed for five seasons. Paralytic poliomyelitis has been observed in persons vaccinated with three doses of the formalin inactivated virus. Faecal specimens were obtained within 14 days of onset of illness in 103 such patients, and the viruses identified in all but 28 specimens. Serum antibody levels in 2709 children who had received three doses of vaccine were studied, and also in blood samples taken after the fourth dose of vaccine in 525 persons. The investigations showed that immunization had been most effective with type 2 virus and least effective with type 3. The fourth dose of vaccine gave a substantial rise in antibody titre, and it was thought that failure of protection in those who had developed paralytic poliomyelitis was probably due to the use of vaccines of insufficient strength, in that of 2700 vaccinated children, 9% had no antibody to type 1 virus, 0.5% no antibody to type 2 and 18% none to type 3.

Poliomyelitis Epidemic.

J. G. MOLNER *et alii* (*J. Amer. med. Ass.*, April 18, 1959) describe the Detroit poliomyelitis epidemic in 1958. In Wayne County, Michigan, prior to 1958 epidemics of poliomyelitis were evenly distributed, but in 1958 the great majority of cases, especially paralytic ones, occurred in the downtown area of Detroit. Apart from

this central area cases were nearly all non-paralytic. The paralytic type was most severe among pre-school-age children, 61% of cases having been in children under five years old. Twenty-two patients died, and none of these had received three doses of vaccine. When it was obvious that the incidence had reached epidemic proportions, a vigorous programme of vaccination was instituted, and some two million odd doses of vaccine were given. However, in spite of an energetic publicity campaign the public did not respond very well, especially for the second and third doses. Personal contact by the public health nurses was suggested, but there were not enough nurses.

Apparent Recovery in Chronic Lymphocytic Leukæmia.

C. REICH (*J. Amer. med. Ass.*, May 9, 1959) reports the case of a 52-year-old woman with a proved diagnosis of chronic lymphocytic leukæmia, who experienced sudden relief from splenomegaly and other signs and symptoms of the disease, and has remained free from all manifestations of the disease for more than five years. The author states that a few cases of apparent recovery have been reported, but that the diagnosis was usually doubtful, and reviewers of these cases have always mentioned them with reservations. During the two years after her condition was diagnosed, the patient received transfusions totalling 22.5 litres of whole blood as well as radiotherapy, but her condition showed no change for the better. The diagnosis was confirmed by lymph-node biopsy and bone-marrow smears. She then went on a visit to her native land (Ireland) and during her two-months' absence experienced a dramatic and complete remission of all signs and symptoms, which has persisted ever since. The author comments that it is possible that the patient is in a period of prolonged remission, but that the case demonstrates that there is hope even in such a dread disease as leukæmia.

Hæmoptysis in Tuberculosis with Emphysema.

I. G. EPSTEIN *et alii* (*Dis. Chest*, May, 1959) state that in a series of 22 patients suffering from chronic active pulmonary tuberculosis with emphysema, who were treated with anti-tuberculosis drugs and prednisone, none suffered hæmoptysis in the course of treatment, although 10 of them had a previous history of repeated hæmoptysis.

Toruloma Producing Bronchiectasis.

P. PERRUCHIO, R. BRUEL, C. LAGARDE AND J. DELPY (*Presse méd.*, February 25, 1959) report a case of infection with *Cryptococcus neoformans* with unusual clinical manifestations; they have named the condition *toruloma bronchiectasiant*. The patient was a girl, aged 12 years, and the infection was contracted from pigeons. The authors state that apparently complete localization of infection with *C. neoformans* in the respiratory tract is frequently the first stage of torulosis resulting from inhalation of the organism, and may or may not be followed by systemic spread. They state that the most common form is that in which

asymptomatic lesions (rounded masses in the lower half of the lung fields) are discovered by radiological examination, and in these cases surgical removal carries a good prognosis. The present case is a new manifestation of torulosis, and extends the range of mycoses capable of producing megamycetoma that lead to bronchiectasis. Less localized forms with more or less acute pulmonary or pleural symptoms are much more serious. Drugs for the medical treatment of this condition are lacking, except amphotericin B, the use of which is still in the experimental stages. Surgical removal is at present the treatment of choice in the localized forms. A long period of post-operative supervision is necessary because of the possible development, even years later, of extrapulmonary foci latent at the time of surgical intervention.

Trigger Mechanisms in Asthma.

R. H. OVERHOLT (*Dis. Chest*, June, 1959) points out that asthma may be perpetuated by structural abnormalities in broncho-pulmonary segments which act as "trigger mechanisms". Routine X-ray examination usually shows no abnormality; however, especially when the illness was initiated by an attack of pneumonia, or when there are frequent colds which settle in the chest or productive cough or unilateral wheeze or chest discomfort or pain or systemic evidence, such as arthritis, of focal infection, bronchography is called for and may show signs of non-function or malfunction of some part of the lung. Exploratory thoracotomy may reveal pulmonary segments which are less pigmented than the rest of the lung, indicating non-ventilation, or segments which are indurated or relatively inelastic may be discovered. Surgical treatment, consisting of denervation with or without the resection of non-functioning segments, usually proved very beneficial.

THERAPEUTICS.

Tetracycline with Nystatin.

R. LARKIN (*Lancet*, June 13, 1959) describes the results of a trial to compare the side effects of tetracycline alone and those of tetracycline with nystatin. His subjects were 98 patients suffering from mainly acute or chronic respiratory infections; these were divided at random into two groups, 55 patients who were given 250 mg. of tetracycline hydrochloride four times daily, and 43 patients who received 250 mg. of tetracycline hydrochloride and 250,000 units of nystatin four times daily. Gastro-intestinal disturbances were noted in 37 of the 55 patients on tetracycline alone, and in four of the 43 patients on tetracycline *plus* nystatin. Diarrhoea developed in nine of the former group but in none of the latter group. Mycological studies were carried out on 37 of the patients. On the fifth day of treatment rectal swabs yielding positive results for yeasts were obtained from 11 out of 19 tetracycline-treated patients, and from two out of 18 who received the tetracycline-nystatin combination. Oral thrush developed in three out of 19 patients given tetracycline alone but in

none of the 18 patients who received nystatin in addition. The author concludes that in addition to affording protection against the direct invasion of tissue by *Candida albicans*, leading to clinical candidiasis, nystatin can apparently substantially reduce gastrointestinal disturbances during the oral administration of tetracycline, which may be fungal hypersensitivity reactions.

Phenethylbiguanide in the Management of Diabetes.

J. B. R. MCKENDRY, K. KIUVAYTI AND P. P. RADO (*Canad. med. Ass. J.*, 1959) describe their experience with the oral use of the new biguanide called phenethylbiguanide (DBI, PEBG or "Phenformin"). In a series of 58 diabetics a satisfactory response was seen with 35 and in the remaining 23 the drug either failed or produced intolerable side-effects. Of the former patients 23 had previously used insulin and 18 of these were maintained by DBI without insulin. On the whole, obese patients responded better than thin patients, and older patients better than younger. In general, diabetes with lower insulin requirements responded more favourably, although two patients requiring more than 80 units daily were treated successfully with DBI. Side effects were chiefly gastro-intestinal, especially abdominal pain resembling that of peptic ulcer. In general, the drug is useful in the same type of patient as tolbutamide, but is more powerful in its hypoglycaemic action than the latter and can succeed where tolbutamide fails. DBI produces hypoglycaemia in pancreatectomized animals and therefore acts in a different way from tolbutamide. The usual initial dose is 75 mg. daily in divided doses.

The Diuretic Effects of Hydrochlorothiazide.

M. A. SACKNER, A. A. WALLACK AND S. BELLET (*Amer. J. med. Sci.*, May, 1959) discuss the diuretic effects of hydrochlorothiazide based upon a study of the use of this drug in 28 patients, of whom 15 were suffering from congestive cardiac failure, six from portal cirrhosis, four from chronic renal disease and three from hypertension. All of these patients were treated in hospital, and except for two patients who were on ulcer diets, they were given a low salt diet containing approximately one gramme of sodium. Initially, the daily dose of hydrochlorothiazide ranged from 50 to 150 mg., and later this was increased to 100 mg. three times daily. In general, the patients tolerated the drug well, but the most important untoward effect was the development of hypokalaemia which occurred in four patients, and a pre-existing hypokalaemia was aggravated in two additional patients. The exact mechanism by which this drug acts as a diuretic has not been definitely established, but its parent compound, chlorothiazide, appears to inhibit renal tubular absorption of sodium and chloride resulting in a secondary increase in water excretion. Also, some carbonic anhydrase inhibition on the renal tubules is noted, particularly with large doses. Hydrochlorothiazide is a potent oral diuretic agent, and it was found to be most effective in patients with congestive cardiac failure. However,

hydrochlorothiazide offered no significant advantages over chlorothiazide, and it has the same tendency to produce hypokalaemia. Close observation and supplementary potassium given orally largely obviates this untoward effect. Hydrochlorothiazide is of limited value in patients with cirrhosis and renal disease. The tendency to hypokalaemia was found to be particularly marked in patients with liver disease. However, hydrochlorothiazide was found comparable to chlorothiazide in diuretic effectiveness.

Propynylcyclohexanol Carbamate.

CL. LAROCHE, F. CHAIN AND N.-T. KY (*Presse méd.*, March 7, 1959) have studied the clinical applications of a new synthetic non-barbiturate hypnotic, propynylcyclohexanol carbamate (L. 2103). The clinical material consisted of 170 patients suffering from insomnia. In an average dosage of 400 mg., the drug was found to have an hypnotic effect in two-thirds of the cases. Sleep occurred from three-quarters of an hour to one hour after the dose had been taken by mouth, and lasted for six to 10 hours. The average duration of action of the drug was about eight hours. The patients did not complain of drowsiness or other unpleasant sequelae on awakening. A control investigation with a placebo confirmed the efficacy of the drug, and indicated that in certain cases regularization of sleep might be obtained after a few days. The authors conclude that L. 2103 seems to be at least as effective as the best hypnotics known at present, and that it is extremely well tolerated.

Polymixin in Gastro-Enteritis of Childhood.

J. FLEURY AND R. EVREUX (*Presse méd.*, June 13, 1959) report their experience in dealing with an epidemic of gastro-enteritis due to *Escherichia coli* O 111 B4 at the children's medical clinic of the Rouen medical school. The organism was resistant to the usual antibiotics, so the authors tried treatment with polymixin in a daily oral dosage of 25 mg. The results were excellent—the illness was shortened, the mortality rate dropped, the drug was remarkably well tolerated, and the organisms did not develop resistance; but hospital infections continued to occur. With the double intention of instituting treatment before serious clinical states appeared, and of taking action to curtail the epidemic, the authors then began to give the treatment on clinical presumption of infection. Their judgement was rarely wrong, and this early treatment reduced the severity of the illness; but it had no effect on the epidemic. In a third attempt to control the epidemic, the authors began to give the drug prophylactically; a daily dose of 25 mg. was given to all the children in the clinic. The epidemic died out in a few days, and so long as the preventive treatment was given, no new infection occurred. The authors believe that the prophylactic use of polymixin in this way is justified, since the full dose is given; resistant organisms are more likely to be produced by small doses, or by frequent encounters between the organisms and the antibiotic. They also think it likely that polymixin, on account of its bacteriolytic properties, is less likely than other antibiotics to induce resistance.

Congresses.

THE AUSTRALIAN AND NEW ZEALAND ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE.

THE thirty-third meeting of the Australian and New Zealand Association for the Advancement of Science was held at Adelaide from August 20 to 27, 1958, under the presidency of PROFESSOR M. L. E. OLIPHANT, B.Sc., M.A., Ph.D., LL.D., D.Sc., F.Inst.P., F.A.A., F.R.S.

THE SECTIONS.

The Sections represented were: A, Astronomy, Mathematics and Physics (including Optometry); B, Chemistry; C, Geology; D, Zoology; E, History; F, Anthropology; G, Economics, Statistics and Social Science; H, Engineering and Architecture; I, Microbiology, Epidemiology and Preventive Medicine; J, Education, Psychology and Philosophy; K, Agriculture and Forestry; L, Veterinary Science; M, Botany, N, Physiology and Biochemistry; O, Pharmaceutical Science; P, Geography.

PRESIDENTIAL ADDRESS.

Science and the Survival of Civilization.

PROFESSOR M. L. E. OLIPHANT read his presidential address entitled "Science and the Survival of Civilization" at the inaugural meeting held in the Bonython Hall on the evening of Wednesday, August 20. He began by saying that unless science became of humanity and was felt as well as appreciated with the intellect, it might well provide the means for man to destroy his civilization, and possibly all life on this planet. There was no evidence that during recorded history man had made any progress whatever in morality. It was necessary to realize that world-wide unrest and turbulence in the human family was the result of advance in science and technology. He would like to examine some aspects of scientific activity today to indicate how the social results of the pursuit of knowledge were reacting upon science itself and how men of science were being forced more and more to give thought to the implication of their work for human survival and welfare. He then proceeded to discuss the relationship between science and government. He said that the extent of the public recognition of science and the role which it played in formulating national policies were utterly inadequate for the smooth and proper development of a country and a nation such as Australia. He then outlined the relationship between science and government in Great Britain as described by Sir Henry Chisett and said that in Australia a beginning had not yet been made to create instruments of policy which took care of the basic science and technology on which the long-term future depended. It was true that the C.S.I.R.O. had an enviable record of achievement in the application of science to Australia's problems and that it had largely replaced the universities as the home of pure scientific research. It was true also that there was well directed activity in defence research, that there was a Bureau of Mineral Resources and that an Atomic Energy Commission was now at work, but those were peripheral activities of government and did not participate in the foundation of all general policies, almost all of which now involved many elements of science and technology. The creation of an Australian equivalent of the Parliamentary and Scientific Committee in Britain could lead gradually to a new awareness in Commonwealth parliament and government of the social significance of science.

Professor Oliphant went on to say that one of the grave difficulties faced by a large section of the scientific community today was the need to work under conditions of secrecy. Such men were cut off very effectively even from their fellow scientists in other secret establishments. As a result of this professional isolation few men of science of high calibre and with an interest in fundamental science were content to remain in secret work. The situation was serious and could threaten the efficiency of the defences of the free world. Defence science would be healthier if ways could be found to counterbalance the grave disadvantages which prevented general recognition of the quality of men engaged upon such work. He asked why A.N.Z.A.A.S. should not have a section of defence science.

Professor Oliphant said that science had been influenced in several ways by the entry of the state into science and applied science on an ever-growing scale. That had produced greater demand for men of science and greater appreciation of the part which science played in modern living. However, several disturbing results had followed. The rapid expansion of official scientific activity had meant

that staff could be made available only by robbing essential institutions of teachers and research workers. Even in the United States, Britain and Australia, teaching had suffered drastic reductions in recruitment and in the standards of instruction in both schools and universities. A more serious result had been the deterioration of the rigid discipline of science which had insisted upon a most searching inquiry into every experiment or theoretical investigation and had demanded that a paramount duty was to publish all results. Now, however, that insistence upon honesty and openness was challenged, and the challenge came primarily from government establishments and especially from those activities which were associated with defence or with national prestige. That was illustrated by the controversy which raged about the question of the effects of fall-out of radioactive substances. The controversy had brought to light the difference between scientific truths and scientific facts coloured or distorted to accord with some political or emotional belief. Those who believed that atomic bomb tests should cease were apt to exaggerate the effects of radiation due to fall-out from tests. Those who had vested interest in bomb manufacture or who desired the approval of a particular section of political opinion claimed that radioactive fall-out caused no ill effects whatsoever. Such emotional scientific dishonesty was deplorable. There was a growing tendency in both government officials and scientists to make ex-cathedra statements, often in daring contradiction with the facts, and when criticized to hide behind the cloak of security. There was evidence that publication of conclusions which were at variance with an officially proclaimed opinion had been deliberately prevented when scientists carrying out the work were public servants. Such muzzling of criticism was a new and disturbing ingredient in science. Strangely enough it was apt to be practised most extensively by those who were most vocal in their opposition to the undoubtedly lack of democratic freedom in the Soviet countries. A further disturbing feature of present-day science was the growing tendency to boast blatantly of the latest achievements in science or technology. Australians might feel that in such things they were but spectators, somewhat amused by the gymnastics of the colossi in the fields of defence and offence. However, many Australians had been tempted into emulation of the antics which were so foreign to the search for truth. One of the reasons for the development of such an attitude was the almost total absence of scientific journalism in Australia. A primary purpose of A.N.Z.A.A.S. was to improve the public appreciation of science and of its effects upon society. Professor Oliphant feared that its congresses were becoming gatherings of specialists and that they were in danger of losing sight of their obligations to make science known to the people.

Professor Oliphant then referred to the threat of annihilation. He said that of the expenditure of the world on scientific and technological developments of all kinds, some 70% was devoted directly to the war effort. Even though the best brains remained outside the restricted barriers of security, the sheer weight of effort and the lavish expenditure of money ensured that results were achieved. The results in the major countries were enormous, and the world now stood on the brink of catastrophe. The two principal factors responsible for that state of affairs were nuclear weapons and long-range ballistic missiles. The two great nuclear powers now stood armed with H bombs deliverable at a moment's notice and sufficient in number and power to destroy completely the whole of North America and of Western Europe, and to do great genetic harm to the rest of mankind. There was a growing awareness among scientists that they could not divorce themselves from the social consequences of their work. He believed passionately in the scientific method and all that it could achieve to raise the stature of man, but he shared Bertrand Russell's fears that wisdom in the use of science might not prevail.

In conclusion Professor Oliphant said that he would like to make a plea for the reorganization and reorientation of A.N.Z.A.A.S. to make it a better instrument for advancing the understanding of science by the people. At the present time they were in great danger of forgetting the purpose for which the Association was formed. The concept of A.N.Z.A.A.S. as an organ of the relation of science with the society in which it was carried on had virtually disappeared. To serve Australia properly A.N.Z.A.A.S. must be revitalized. It should concern itself with the all-important questions of science and its reactions upon society and of the way science fitted into society. It should be concerned to tell the ordinary man something of the significance of recent advances in science and should make him aware of the basic nature and meaning of scientific activity. It should also enable scientists to

learn of advances in related disciplines. It should not be an occasion for specialist meetings which belonged with the specialist societies. He believed that they could with profit widen the scope of the Association still further, so that it became a common meeting place of scientists and those professing the humanities. Congresses should not shirk discussion of really controversial questions, such as population control, morality in a technological age or the relations between science and religion. He put forward the suggestions because he was convinced that something along those lines must be done, and quickly, if Australia was to be governed by men alert to the problems of the time and elected by informed and intelligent citizens.

PUBLIC LECTURES.

On the evening of Thursday, August 21, Sir Douglas B. Copland, K.B.E., C.M.G., D.Sc., Litt.D., LL.D., delivered the first Giblin Memorial Lecture, in the Bonython Hall. The subject of his lecture was "L. F. Giblin and the Frontier of Research on the Australian Economy".

On the evening of Friday, August 22, Sir Keith Hancock, M.A., delivered a lecture on "War in this Century", in the Bonython Hall.

On the evening of Monday, August 25, Dr. Tara Chand delivered a lecture entitled "India and the West", in the Bonython Hall. Mr. P. G. Law delivered an illustrated lecture entitled "The I.G.Y. and Antarctica", in the Mawson Theatre. Professor J. S. Anderson delivered the Masson Lecture, entitled "The Renaissance of Inorganic Chemistry", in the Rennie Theatre.

SECTION D: ZOOLOGY.

How Many People Can the World Support?

A symposium entitled "How Many People Can the World Support?" was held, PROFESSOR H. E. ANDREWARTHA in the Chair. Professor Andrewartha regretted that Professor W. D. Borrie, who had taken a large part in organizing the symposium and was to have delivered the first paper, had been unable to attend because of an accident.

MR. R. H. GREENWOOD (Queensland) then read a paper on the resource outlook in a world of increasing population. He introduced his remarks with a short account of current population trends in place of Professor Borrie's paper. He pointed out that between 1850 and 1950 the population of the world had more than doubled, and that reliable figures for the increase from 1950 to 1957 showed a rate of increase of about 47,000,000 persons *per annum*. That was an increase at the rate of 1.6% *per annum*, which if it continued would double the world's population by the end of the century. He concluded this part of his paper by quoting from Professor Borrie: "The great upsurge of the world's population in recent years derives therefore from the great changes occurring in the Afro-Asian section. The major question is whether the cycle of growth set loose by the control of mortality can be short-circuited. Events in India and China are not at first sight encouraging, but the very rapid move towards low fertility in many other parts of the world (e.g. the Soviet Union, Italy, Japan) provides more grounds for hope. There is also reason to believe that advances in medical sciences may yet produce some form of control that will find very little resistance in the social and cultural mores of the great populations of the Asian world. Before control can be effected, the world's population may well double, but this need not necessarily be a tragedy."

Mr. Greenwood then proceeded to discuss the outlook for food and other resources in a world of increasing population. He stated that objectivity was difficult; the optimists on this question tended to come from the crowded countries of Europe and Asia, and the pessimists from America. Thus some authorities viewed the prospect of a world population of ten to sixteen thousand million with equanimity, whereas William Vogt, an American, believed that it was obvious that fifty years hence the world could not support three thousand million people at any but coolie standards for most of them. Mr. Greenwood then considered the various estimates of the proportion of the earth's surface which might be cultivated. It was very hard to see why it should not be possible to treble farm production in the current century, but the ability to produce food must be matched by the ability to pay for it. In India, in spite of the increase in population, food production had increased little. Production per head had actually fallen, imports of rice had fallen, and the daily caloric intake had fallen from 2000 to 1700 Calories. Since 1957 a very considerable flow of money, equipment and food to Asia under the Colombo Plan had gone some way to maintain the *status quo*, but the aid appeared to have been dispersed among too many people to have brought significant relief to any.

Mr. Greenwood asked whether one might then say that the problem of feeding India was insoluble. He believed that the solution lay along five lines. First, the Asian population should be spread over a larger area; at present Asia contained both overcrowded and vacant areas. Second, a programme of organization and industrialization must be undertaken. Third, the western world should produce more food for the east. Fourth, some way of manipulating currency to cheapen imported food should be found. Last, some form of birth limitation in combination with increased food supply seemed the only chance of raising living standards. It was evident from all this that India's economic problem was not a national but an international one. Mr. Greenwood then commented briefly on the future of supplies of other raw materials. He concluded by saying that in his view there could be only one general conclusion. For humanity to survive, population increase must be accompanied by accelerated technological progress. For the foreseeable future there could be food and resources enough provided that the barriers to trade between the east and the west, between the cool world and the tropics, were lowered, and provided that all nations would recognize the rights of others to economic expansion without cherishing the out-dated idea that economic growth was necessarily synonymous with political expansion.

MR. E. A. RUSSELL (Adelaide) then read a paper on some economic aspects of world population. He said that western Europe and its offshoots in the Americas and Australasia, together with the U.S.S.R. and Japan, had achieved a rate of increase of output in excess of the rate of the increases of population, so that real income per head was increasing per century. Those countries contained rather more than a quarter of the world's population. The rest of the world had for long periods been unable to increase total output at a greater rate than population, so that real income per head was stagnant. Recent statistics showed that the divergence between the advanced and the undeveloped countries was continuing. In 1938 the offshoots of western Europe enjoyed an income per head four times the world average; by 1949 that had risen to six times the world average. In 1938 the income per head in southern Asia was one third of the world average. In 1949, that had fallen to one-fifth of the world average. The question "How many people can the world support?" was misleading if it implied some limit imbedded in nature to the output of food and goods. An alternative was to ask what would be the possible output of food if certain levels of techniques were adopted, and how many people could be supported at a certain specified standard of life. It had been estimated that twelve billion people could be supported at Danish standards if Danish methods of production were universally employed. Such estimates showed that space, soil and climate were not rigid limits to population growth, but the important questions were avoided. To achieve such levels required intensive economic and social changes. The crucial question could be posed only if it was seen that the rate of population growth and the rate of the increase of output were not independent but were related in a complex way. There could be a world population of five and a half billion in A.D. 2000, with a large proportion of the world's population living near the subsistence minimum. There could be a population of more than six billion and yet the problem of population pressure on resources could be on the way to solution. Rising living standards tended to increase the rate of population growth in the early stages, which meant that total output must increase at an even greater rate. Population increase in that view acted as a hurdle yet to be cleared. By huge effort, increases in national output must be telescoped into a short period. After discussing the percentage of the total income which had to be invested to provide for the extra population, and to increase output per head, Mr. Russell said that the difficulties facing India, China, Indonesia and so on were immense, and in some ways greater than those formerly faced by western Europe. The great fall in the death rate which had taken place in some underdeveloped countries in the postwar period had been largely independent of any initial improvement in the standard of life. Some people regarded the facts with pessimism and argued that a prerequisite of economic advance was an independent check to population growth from the start. However, for many obvious reasons, birth rates were not easily manipulated. There were other possibilities besides varying the population growth. One was to increase the proportion of national income going into investment, without first greatly increasing total output. Another was to increase output independently of capital accumulation, and to devote a high proportion of the increase for further accumulation. The question of how many people the world could support was therefore seen to turn into the question, "What are

the chances of economic development for the dispossessed 70% of the world?". Population limitation policies in the countries concerned would take their place as one of an interconnected series of measures to initiate economic development.

DR. G. E. M. MAYO (Adelaide) discussed the question from the point of view of genetics. He stated that human progress was determined, not only by political and ethical forces but also by the laws of biology. It had been suggested that human biological evolution had ended and had been replaced by the evolution of culture, and that natural selection no longer operated in modern man. But to the biologist, the analogy of the now very large experience with living organisms provided a powerful and valid tool for setting up useful models for human populations, capable of being tested by the collected evidence. It was on that basis that Dr. Mayo wished to approach the problem of world population. He said that there was a quickening interest in human biology, mainly in the field of human and population genetics, so that the discussion could be claimed to be timely. After discussing human genetics as it might have operated in the past, Dr. Mayo said that two general suggestions seemed to be relevant in considering the human population of the modern age. The first concerned the quality of the structure of the population. It could be argued that the general mutation rate would be higher in the modern urban population, while at the same time the Welfare State meant a relaxing of natural selection. That led to the idea that detectable, measurable and, following the appropriate work, predictable biological influences contributed to the different population trends. The second suggestion dealt with the relationship of selection and migration in a population. The organization and development of a population was a complex affair, but biologists' experience did suggest that the determining factors could be studied individually so as to lead to a fairly clear picture of the related parts played by the various influences on the abundance or scarcity of human populations. The proper understanding of *Homo sapiens* as a biological species could provide a sound basis for work in the social and economic disciplines.

The Biological Effects of Radiation.

Opening a symposium on the biological effects of radiation, DR. E. P. GUNN (Sydney) discussed the physical aspects of the subject. He began by summarizing the different types of radiation and the units in which they might be expressed. He then discussed the biological effects caused by the ionization of tissue proteins within the cell. He said that it was at least possible to say how much radiation produced certain effects; for example, mitotic inhibition was caused by 100r, chromosome breakage by the same amount, genetic mutations by 10r to 100r, etc. He then summarized the radiation levels at present being experienced by man from such sources as medical X rays, industrial radiography, background radioactivity and radioactive fall-out, and emphasized the differing tolerance levels for occupation and whole population exposures. He stated that it was necessary to educate clinical colleagues in an appreciation of the importance of minimizing exposure to diagnostic radiation and discussed the hazards involved in the diagnostic and therapeutic use of radioisotopes.

DR. A. N. CLARK (Melbourne) then read a paper on the genetical effects of radiation. He stated that the precise nature of the mutations induced by ionizing radiation was still not clear; although it had been widely assumed that they were qualitatively equivalent to spontaneous mutations, the evidence was conflicting. However, the dose-effect relationships were well established. There was some evidence that at very high doses the simple linear relationship might reach a plateau, suggesting some kind of saturation effect in the ability of the organism to show mutational response. The effect of radiation might be modified by inhibitors of metabolism such as cyanide, carbon dioxide or low temperatures. Variation in radiation sensitivity of cells at different stages in spermatogenesis, together with modification of genetic effects by altered experimental conditions, emphasized the inapplicability of simple target theory considerations and suggested a complex series of reactions intervening between the absorption of radiant energy and the final genetic effect.

DR. W. P. HOLMAN (Melbourne) then read a paper on the use of radioactive chronic phosphate in the treatment of malignant serous effusions. He said that the management of patients whose uncontrolled malignant diseases led to ascites was difficult. In the past X-ray therapy had been useful, but the side effects were severe. Cytotoxic drugs had been used, and benefited a proportion of patients, but

their use was limited by the effect on the marrow. Studies of tritium-labelled water showed that in a patient with ascites upwards of 100 litres of fluid might be transferred across serous membranes in 24 hours. The problems involved were complex and the mechanism of action of radioactive isotopes or of cytotoxic substances was not well understood. Radioactive gold salts had first been used. They emitted a combination of beta and gamma radiation, but the latter was undesirable and dangerous. Radioactive phosphorus gave out no gamma radiation and had a longer half life. Latterly, radioactive chromium phosphate had been widely used in the United States, but till recently it had not been used in the United Kingdom because of possible danger to the bone marrow. DR. HOLMAN described the method of administration of this substance and went on to discuss the results of its use to irradiate ascites tumour cells in mice, in an endeavour to arrive at a satisfactory dosage level for clinical purposes. In mice it did not influence the survival time, but it did reduce the accumulation of ascitic fluid. He then described the results obtained in the treatment of a small group of patients. Ten had been so treated so far, and the results were encouraging. In only one case was failure complete. The absence of tumour masses in the abdomen was important. He thought that it was desirable to have some substance more physiologically inert than chromium phosphate.

DR. EVA EDEN (Sydney) then read a paper on the effects of radiation on the physiology of the cell. She said that there was still much that was not known about the biological and physical effects of radiation on cell mechanisms. Radiation had a direct effect on the macromolecules of the cell, but also on water and on small molecules, which had an indirect effect on the macromolecules. In addition, repair processes depended on a very large number of different factors. Several lines of investigation were open. Among the most interesting of those was the work done on the synthesis of nucleoprotein, and on attempts to separate nuclear and cytoplasmic effects of radiation. It had been concluded that the nucleus was about two to four times more sensitive than cytoplasm. DR. Eden described the technique by which Davies and others had been able to irradiate one part of a cell at a time. Combined with microbiological methods, that might give very useful results. She then discussed the various forms of protection against radiation. First there was the chemical protection afforded by certain substances, which had to be given before exposure to radiation. Then there was protection by replacement therapy, involving the transplantation of cells from spleen or bone marrow, which, however, would survive only after the host cells had been destroyed by radiation. The applicability of such cells and the difficulties of storing them, but it would be interesting to see what avenues further work might open up.

SECTION F: ANTHROPOLOGY.

Timing in Human Evolution.

PROFESSOR A. A. ASIM (Adelaide) said that the physical features which distinguished man from other primates, and different human groups from one another, while genetically determined, were manifested in the differences in timing such features were accorded in their onset, in the duration of development and in the cessation of development. Relative retardation in differentiation was pedomorphism, acceleration was gerontomorphism; a mixture of the two processes produced the final distinctive results. In man, as compared with apes, pedomorphism was outstandingly evident in the skull and brain, in the jaws and teeth, in the superior extremities, in the onset of ossification, hair development and pigmentation, in the period of gestation, in onset of maturity and in expectation of life. On the other hand, some features, such as the inferior extremities (apart from the toes) and orthograde adaptations in the thorax, vertebral column and pelvis, were gerontomorphic. Nevertheless, the human as a whole was predominantly pedomorphic in comparison with apes. Amongst human groups, those which betrayed a more infantile stage of development—many pygmies, dwarfs, mongoloids etc., with relatively round heads and short inferior extremities—were pedomorphic compared with Europeans, who, in turn, were pedomorphic over-all compared with longer-legged and longer-headed peoples such as many African groups and the Australian aborigines. In aborigines such pedomorphism became evident from about the sixth year. In all groups adult females were pedomorphic compared with adult males. Pigmentation in coloured peoples was an example of gerontomorphism, but must be attributed to natural selection, not to "sub-human".

affinities. Timing in differentiation might be upset by endocrin disturbances.

Haemoglobins, Haptoglobins and Ethnology.

DR. O. E. BUDZ-OLSEN (Brisbane) said that the history of the abnormal haemoglobins began only in 1948, when Pauling demonstrated the molecular difference between normal and sickle-cell haemoglobins. Since then more than a dozen abnormal haemoglobins had been found, all confined to Asia and Africa, with a small spread into Greece and Italy. The haemoglobins had the same characters as the blood groups, which made them useful as ethnological tools: their inheritance was simple and depended on a few single genes; they were not changed by environment, except perhaps by balanced polymorphism in some areas; their determination was simple and well suited for large surveys. Present evidence suggested that the mutations giving rise to the new haemoglobins had taken place in some part of southern Asia; from there they spread to neighbouring territories and, in the case of the sickle-cell haemoglobin, to Africa. It would appear that that spread had taken place in fairly recent times, as no abnormal haemoglobins were found in Africa south of the Zambezi River. On Madagascar, with its originally Indonesian population, only sickle-cell haemoglobin was found, and the gene had undoubtedly been brought there from Africa in fairly recent times. The question should be considered whether, with further study, it might not be possible to put an exact date to the first appearance of the new haemoglobins, and thereby enhance their anthropological use.

The story of the haptoglobins was even shorter. There were two types, and their genetics and determination were simple. Surveys in America, Europe and Africa had shown distinct differences in the haptoglobin groupings of Europeans and Africans. In Australia two surveys, one among Central Australian aborigines, the other among North Queensland aborigines, had given groupings quite different from those of Europeans and different from each other. The picture at the moment was confused, but there was little doubt that in the future serum proteins would take their place with blood groups and haemoglobins in ethnological surveys.

Blood Groups of Australian Aborigines.

DR. R. A. BARBOUR read a paper prepared by DR. R. T. SIMMONDS (Melbourne) discussing the blood-group genetics of Australian aborigines. Dr. Simmonds first discussed the various theories of Australian origins. In one view the Australian aborigines represented a major race, characterized by a remarkably uniform physical morphology, who were the first representatives of *Homo sapiens* to wander out towards the Pacific. Other views regarded them as the result of the mixture of several distinct migrations. According to the tri-hybrid theory, three main ingredients were involved, typified by the Barrineans (who were oceanic negritoes), the Murrayans and the Carpentarians. However, no distinctive differences between the blood groupings of the three elements could be demonstrated. Dr. Simmonds concluded that it was not possible to say from laboratory data alone whether there was a single or triple origin for the Australian aborigines, but he presented the collected data as a basis for further discussion.

Blood Pressure, Serum Cholesterol and Atherosclerosis in Australian Aborigines.

DR. J. R. CASLEY-SMITH (Adelaide) said that two of the chief causes of death among Europeans were high blood pressure and atherosclerosis. The Central Australian aborigines had low blood pressures, low serum cholesterol levels, low serum mucopolysaccharide levels, and a low fat diet. The diet of tribal natives was also low in salt content, and such diets had been found to be associated with low blood pressures among the Chinese, among poor fishing villagers in Japan and among some African negroes. Under primitive conditions the Australian aborigines had a low incidence of atherosclerosis. In general it might be said that in tribal Australian aborigines the diet content of animal fat, salt and total calories all varied with the blood pressure values. Cholesterol levels, mucopolysaccharide levels and blood pressure all rose with increasing urbanization.

SECTION Ia: MICROBIOLOGY, EPIDEMIOLOGY AND PREVENTIVE MEDICINE.

Latency in Viruses.

In his presidential address to the Section of Microbiology, Epidemiology and Preventive Medicine, PROFESSOR J. A. R. MILES (Otago) spoke on latency in viruses. He said that

it was common for viruses to be present in host tissues for prolonged periods without giving rise to any symptoms, and that such viruses were commonly said to be latent. In the present discussion he proposed to say something about knowledge of the viruses carried by bacteria and to relate that to the little that was known about the carriage of viruses by animals. In bacteria there were two separate types of relationship between host and virus. The first was the lysogenic state, in which the virus in a masked form was incorporated into the genetic mechanism of the host cell and caused lysis of only a very small minority of infected host cells. The second was the carrier state, in which a resistant host, throwing numerous susceptible mutants, maintained an uneasy equilibrium with the virus. Professor Miles then proceeded to examine some of the host-virus systems in warm-blooded animals which had been investigated and to consider whether latency in animal viruses might involve mechanisms similar to either the lysogenic state or the carrier state. During the last ten years at least fifty viruses of human origin had been identified, and there were probably hundreds of other unidentified agents. Some of the new viruses could become latent in man, but it was not clear that all of them could do so, and none had been sufficiently studied. More could be learnt from consideration of those animal viruses which had been known for a long time and which had been investigated as to their capacity to become latent. One of those was lymphocytic chorio-meningitis of mice. In the latent form it had been shown that, although the animals carried amounts of the virus throughout life, they developed no demonstrable antibodies against it. It had been suggested that this was due to failure to recognize as foreign substances introduced during fetal life. It was interesting to speculate on the similarities between this situation in mice and that of homologous hepatitis in man. In both examples virus was present in the host, not readily transmissible by natural means and doing no harm to the host. In the one case mature virus was already present in the blood-stream, and in the other probably only rarely. It was possible that the viruses existed predominantly in a provirus form, but it might be unnecessary to postulate the provirus form but necessary merely to assume a production of virus so slow that it did not seriously upset any organ in the host and, in the absence of circulating antibodies, the virus could survive for a relatively long time in the blood. Professor Miles said that herpes simplex was a classical example of a virus latent in man. It appeared to remain in the deeper layer of the epithelium throughout the life of the individual, but it could be activated and become apparent through some such agencies as fever or even after exposure to ultra-violet light, and it was natural to compare this with lysogeny in the bacteriophage system. However, evidence had recently been brought forward to suggest that a different mechanism existed which could account for the observed phenomena. In conclusion Professor Miles said that he had merely selected a few examples of systems in which inapparent infection with an animal virus could continue for a long time, and had attempted to compare those with latent infections of bacteria with bacterial virus. He had tried to show that there might be conditions in animals similar to the carrier state in bacteria, but he had offered evidence that at least in the case of herpes simplex there might be a mechanism for survival quite different from any known in bacteria. He did not claim to have any evidence that no animal virus could enter into a state comparable with that of prophage in its bacterial host, but he did not think that in the example that he had examined there was any good evidence that such a state did occur.

Myxomatosis.

DR. I. D. MARSHALL (Canberra) discussed recent trends in the host-parasite balance in myxomatosis. He said that myxomatosis had offered a unique opportunity for studying the balance between a virus and its host in a natural environment. There was an approximate relationship between the mean survival time of small groups of laboratory rabbits infected with myxoma virus strains of differing virulence and percentage mortality produced by those strains in large groups of rabbits. This had made possible the assessment of the virulence of numerous strains of virus collected each year throughout Australia. Although strains of greatly reduced virulence had become relatively common in recent years, strains which would kill about 90% of susceptible rabbits continued to dominate the field. Evidence had recently been obtained that suggested a change in the roles of dominance of two soluble antigens produced during the course of the disease.

Alterations in the genetic resistance of wild rabbits had been studied by sampling the young progeny of selected wild populations, and after rearing them to the age of four months, challenging them with virus strains of known virulence. The evidence for the emergence of races of rabbits with significantly greater innate resistance to the disease now seemed unequivocal, and the degree of resistance exhibited by a population was related to the number and intensity of epizootics which it had experienced, showing that evolution by selection under natural conditions could be quite rapid.

Pathogenic Coliforms and Paracolons.

DR. ROSS MUSHIN (Melbourne) said that some serotypes of *Escherichia coli* were not infrequently isolated from cases of infantile gastro-enteritis and were considered by many workers as specific aetiological agents. The geographical distribution of those strains was apparently very diverse. Her present studies were based on an epidemiological survey, and included the examination of fecal specimens from isolated cases of gastroenteritis, from children in institutions and from normal babies. Most of the subjects examined in the investigation were under the age of one year. It was found that prevalence of pathogenic *coli* in some nurseries was high; for example, certain serotypes were isolated from 48% of cases. It was evident that the cross-infection rate with those organisms could be exceedingly high. A great variation in response to infection with serotypes had been observed, in that some babies carrying the organisms were symptomless, and others exhibited signs and symptoms of severe gastro-enteritis. The distribution and the possible reserves of serotypes of *E. coli* had also been investigated, and they had been isolated from dogs, calves and possums. Their ecology was the subject of further study. Paracolon bacilli might be isolated from normal and pathogenic stools. In normal fecal specimens they were present in small numbers, while in abnormal stools their ratio to the normal coliform flora was high.

Genetic Recombination with Vaccinia Virus.

PROFESSOR F. J. FENNER (Canberra) said that one of the most interesting advances in genetics in recent years had been the contribution for the first time of data from the study of microorganisms. The genetics of animal viruses was still in its infancy, and had as yet made no impact, but when certain problems were solved, its impact would be very important. The technical aspects of the study in vaccinia virus had reached a stage when collaboration with geneticists and cytologists could be fruitful. The three essentials for the adequate study of genetic recombination between animal viruses were (a) cell systems in which one or more cells could be infected with the two parental strains, (b) related strains of the virus which differed in at least two independent well differentiated marker characters, and (c) a method of recovery from mixed-infected cells of virus clones which were derived from single viral particles. Those requirements were satisfied by certain strains of vaccinia virus grown in the egg, in mice or in tissue culture, and assayed on the chorio-allantoic membrane. Three of the five marker characters available were virulence markers. They were complex and probably not independent. The other two markers, products of a particular antigen and resistance to heat inactivation, were independent of the virulence markers. Recombination could now be regarded as an incontrovertible fact, and was found to be a relatively common consequence of mixed infection in all the cell systems examined. It seemed to him that the stage was now set for the geneticists to enter into collaboration with the virologist.

Cell Structure As Revealed by the Electron Microscope.

DR. J. D. MACLEAN read a paper on cell structure as revealed by the electron microscope. He said that until recently electron microscopic evidence concerning cell structure has been regarded sceptically by a large proportion of biologists. In view of the unsatisfactory nature of the earlier techniques, which relied largely on fragmentation, that attitude was understandable. With the development of techniques for preparing suitably thin tissue sections, the discipline was regarded as respectable by all except a few. However, the interpretation of electron micrographs was difficult unless one was familiar with the manner by which they were obtained. He described the techniques used for fixation and embedding with emphasis on the differences between the techniques described and those of conventional cytology. The contrasts seen in the electron microscope image were functions of the electron scattering properties of matter. They did not depend on

absorption of electrons in the way that the conventional light microscope depended on the absorption of light. To some extent they resembled the contrast given by the phase light microscope. In the case of non-periodic objects the only direct way of checking the reality of the cell structures revealed by the electron microscope was by means of phase microscopy of living tissue, which was of course restricted to low resolution. For periodic objects, such as protein crystals, chloroplasts, muscle and nerve myelin, X-ray diffraction by living tissue had been used to confirm the reality of the electron microscope picture. It was therefore a reasonable assumption that non-periodic structures made visible by the electron microscope also had a real existence in the living cell.

SECTION 1: NUTRITION SUBSECTION.

Whole Cow's Milk as a Food for Infants.

DR. R. A. MACMAHON (Newcastle) read a paper prepared in conjunction with DR. JOAN WOODHILL and DR. R. M. GIBSON on whole cow's milk as a food for infants. This work has since been described in a paper published in this journal.¹

Celiac Disease and Nutrition.

MRS. R. C. RANKIN (Melbourne) said that studies of celiac disease in children had been going on since the beginning of this century, but that until the work of Dick, published in 1950, on the relationship between wheat flour and celiac disease, treatment involved the use of very simple diets, such as the banana and fruit diet. Treatment now involved complete elimination of all wheat and wheat flour from an otherwise normal diet. Work in several centres, including the Royal Children's Hospital, Melbourne, had aimed at determining the reason for the effects due to wheat flour. It had been found that whole flour, wheat flour minus the carbohydrate and phospholipid fractions, a peptic digest of gluten and the water-soluble dialysate of this, all caused the characteristic symptoms of steatorrhoea and anorexia in test patients. Amino acids, obtained by either enzymatic or acid hydrolysis of wheat gluten or glutamic acid alone, gave no symptoms. Wheat gluten had been shown not to act as a typical allergen, thus disproving the allergy theory. Another theory which had been recently suggested postulated the importance of peptides containing glutamin, possibly owing to the absence in the small intestine of a specific mucosal peptidase which might deaminate those peptides. It was also possible that removal of glutamin peptides from the blood-stream by the liver might be impaired and that the primary defect lay there.

Diets Self-Selected by Children in Hospital.

MISS JANET WINN (Newcastle) read a paper on the inadequacy of diets which had been self-selected by children in hospital. She said that the feeding of children in hospital was more than a problem of supplying adequate nutrition. When a child was admitted to a hospital, being removed from his familiar environment might produce quite a marked effect on appetite. In some circumstances any attempt to use force in feeding the child might result in refusal to eat. In 1931, Davis, in Chicago, had evolved a system in which children were allowed to select their food, and the results were considered completely satisfactory. From his report and from other observations of children on closely selected diets the system now used for the older children at the Royal Newcastle Hospital had been evolved. In the system children were offered a limited selection of food, from which they were allowed to choose any food they wished, even if that meant that the meal consisted of only one item. A record was kept of the foods chosen by each child and the number of servings eaten. In that way an approximate nutritive intake might be calculated at any time. In the survey described, 90 complete intakes had been collected. The children had been divided into three groups according to age and sex. It was found that in each case approximately 50% of the children had an intake which was good or excellent. In the remainder the intake was classed as fair, poor or very poor. Diet was assessed on the intake of seven constituents as follows: protein, calorie, vitamin A, calcium, thiamine, ascorbic acid and riboflavin.

MRS. AUDREY CAHN (Melbourne) read a paper, prepared in collaboration with Miss Katherine Neal, on further findings on the nutritional and dietary aspects of the Melbourne Child Growth Study. She said that the project consisted of a longitudinal study of the physical growth of a selected group of normal children of Australian parents residing in the Melbourne area. The preliminary findings

on the nutritional and dietary aspects of the study had been presented at the previous ANZAAS meeting. In the present paper she presented the results of the investigations during the second and third years of the study and conclusions drawn from the findings of the three years as a whole. The dietary survey had consisted of an assessment of a record of food consumed by each child throughout one week of every year. Mrs. Cahn then described the technique by which this information was obtained. It was found that the majority of dietary inadequacies arose from behaviour problems when the child passed through a stage of aggression and assertion. A small percentage of mothers showed gross ignorance or indifference to diet. The extent of vitamin supplementation, either regular or seasonal, was surprising. At the first visit it was found that 40% of the girls and 21% of the boys were receiving vitamin supplements. At the second visit the figures had risen to 45% and 31% respectively. An assessment was made of the refined carbohydrate intake, and this was correlated with the incidence of dental caries. The caries incidence increased with age, and the number of children free from caries declined at five years of age, but the fall was much more rapid in those children with an excess of refined carbohydrate in their diet. There was a consistent finding of a higher prevalence of caries among those children taking diets in which refined carbohydrate was high.

Thyroid Function in Pregnancy.

Dr. D. WINIKOFF (Melbourne) read a paper, prepared in collaboration with R. D. DICKINSON and G. WADE, on the results of an investigation into the level of circulating thyroid hormone in pregnancy, as measured by the total protein-bound iodine (PBI) and globulin-bound iodine (GBI) serum levels. She said that the commonly used indices for the assessment of thyroid function were the estimation of the basal metabolic rate, the uptake of radioactive iodine and the chemical determination of protein-bound iodine (PBI) or butanol extractable iodine (BEI) of plasma. In normal pregnancy all of those were above the normal euthyroid levels without any clinical evidence of hyperthyroidism, and some investigators believed this effect to be secondary to the rise in oestrogen output. However, in recent years the concept of change in the transport of thyroid hormone by the plasma proteins suggested a possible explanation. In cases of habitual abortion the enhanced capacity of thyroxine-binding globulin to bind added radiothyroxine, demonstrable in normal pregnancy, was not present. The chemical estimation of globulin-bound iodine (GBI), originated in their laboratory, offered an alternative method without the use of radioactivity.

Twenty cases of normal pregnancy (65 tests), 24 cases of habitual abortion during pregnancy (35 tests) and four cases of first spontaneous abortion (4 tests) had been investigated. The mean PBI and GBI levels for normal pregnancy were 7.6 mg. and 2.1 mg. per 100 ml. respectively. Those were considerably elevated above the normal levels of 5.2 mg. and 1.2 mg. per 100 ml. in non-pregnant individuals. In cases of habitual abortion both PBI and GBI values were considerably below the normal pregnant levels (6.5 mg. and 1.3 mg. per 100 ml.), and the differences were statistically significant. The GBI values showed the trend more clearly than total PBI values. On account of the marked degree of overlap the test could not be used at present to predict the outcome of an individual pregnancy, but a GBI value below 1 mg. per 100 ml. would suggest the possibility of abortion impending, while a value of above 2.1 mg. per 100 ml. would almost exclude it. Intramuscular progesterone depot administered to four healthy non-pregnant individuals did not produce any effect on PBI or GBI levels. Dr. Winikoff considered that concurrent determinations of GBI and blood progesterone or urinary pregnanediol levels could offer a better chance of evaluating the prospects of the preservation of pregnancy.

Medical Matters in Parliament.

NATIONAL HEALTH BILL, 1959.

THE following is the second reading speech by Dr. the Hon. D. A. Cameron, Commonwealth Minister for Health, delivered in the House of Representatives on October 22, 1959.

The last few years have seen great growth and development in the National Health Scheme established by this Government. To take two examples, payments of Common-

wealth and fund benefit in the Hospital Benefits Scheme have now reached £25,000,000 per annum, whilst benefits payments in the Medical Benefits Scheme now exceed £17,000,000 per annum. These benefits flow directly to patients, enabling them to meet the major part of their hospital and medical costs.

It is of course a matter of great satisfaction to this Government that there has been such strong public support for the purely voluntary scheme which we initiated and fostered. There is no doubt whatsoever that a contributory health benefits scheme on a voluntary basis is the one most appropriate to Australian needs and conditions, and that the future of this scheme is now assured.

At the same time the Government recognizes that growth and development necessarily give rise to new problems and it is to deal with a number of such problems that this Bill is introduced. It will, I think, be most convenient if I deal with the various matters in relation to the particular aspects of the National Health Scheme which they affect.

Medical Benefits.

The Treasurer announced, in his Budget Speech on August 11 last, that the Government intended to negotiate with registered medical benefit funds with a view to introducing a plan for considerably higher Government and fund benefits for major surgery and certain other medical services. These negotiations were commenced within a few days of the Treasurer's announcement, and I am happy to inform the House that they have led to the formulation of a plan under which medical benefits will be substantially increased for many surgical operations and other costly medical services.

This Bill provides for increases in some 140 items in the Schedules of medical benefits. The largest increases are for major operations, where the Commonwealth benefit will in some cases be increased from £11 5s. to £22 10s. The benefit for many of the less serious operations will be likewise appropriately increased.

Whilst the increases in Commonwealth medical benefits will thus be implemented by this legislation, the increases in fund benefits will be effected in different ways according to the particular circumstances of each organization. The largest medical benefits organizations in New South Wales and Victoria have agreed with me that they will soon introduce new tables providing fund benefits related to the new Schedules of Commonwealth medical benefits, and contributors will be invited to transfer their insurance coverage to these new tables. Many of the other organizations will implement the new arrangement simply by making an increase in the rate of contributions payable by their contributors.

The amount of the increase in the rate of contribution will depend on the amount of the increase in fund benefits provided by each organization. This will vary from organization to organization. In many cases the organization will increase its fund benefit by the same amount as the Commonwealth benefit is being increased, and, in these cases, the rate of contribution will rise by about 6d. per week for a family and 3d. a week for a single person. In other cases the organization may increase fund benefits by amounts considerably in excess of the increase in Commonwealth benefits, and where this is done the rate of contribution will of course have to be increased by a greater amount. Before the plan comes into operation on January 1 next, every contributor will be able to get exact information from his own organization regarding the cost of insuring for the new benefits.

Commonwealth benefits at the new increased rates will be payable to contributors who are insured for fund benefits equal to those set out in the First Schedule to the *National Health Act* as being amended. However, in order to allow adequate time for contributors to adjust their insurance, where necessary, so as to become eligible for these benefits, the Bill provides that during the first year of the operation of this plan, insurance at a level equal to the present First Schedule will constitute eligibility for Commonwealth benefits.

This amendment is an extremely important one. Although the number of persons who have to undergo major surgery is relatively small, compared to the total number insured, the burden of the medical fees in these cases can be extremely heavy. Under this new plan, however, it will be possible to insure against this burden by joining a medical benefit table which in the case of major surgery will provide Commonwealth and fund benefits up to £60 for a major operation. Up to date the maximum benefit payable for any one operation has been £30. Thus, in one step, we are implementing a plan which will double the

benefits payable to contributors for these serious operations for a small increase in the weekly contribution. I feel confident that members of medical insurance funds will be pleased with this new arrangement and will take advantage of the opportunity provided to insure themselves adequately against the risk of major surgery.

Medical Benefits Special Accounts.

The other medical benefit amendment proposed by this Bill is of a technical character. It is of considerable importance to the medical benefits organizations, but of little significance to contributors. Briefly, this amendment will relieve medical benefits organizations of the obligation to transfer contributors for medical benefits to the special account upon reaching the age of 65. It was initially thought that the over-65 contributor was causing an undue drain on the funds of the medical benefits organizations, and accordingly we agreed last year that these persons would be enrolled in the special accounts guaranteed by the Commonwealth.

Experience has, however, suggested that because of the coverage provided by the Pensioner Medical Service the over-65 contributor has not, in fact, drawn unduly heavily on the medical benefits funds. The organizations are therefore prepared to carry this class of contributor in their ordinary accounts, and this Bill will enable them to do so. This provision will have no effect on contributors because the Funds will continue to pay them the full benefits to which they are entitled under the Funds' rules, and, in the event of a preexisting ailment or maximum benefit rule disqualifying them from fund benefit, they will then be transferred to the special account and receive medical fund benefits from the special account in the same way as any other contributor. I hope it will be clearly understood that the requirement that contributors shall be automatically transferred to special account on reaching the age of 65 is being removed for medical benefits, but not for hospital benefits.

Hospital Benefits.

In regard to hospital benefits, one amendment only is proposed. This is in relation to a matter on which there has been a great deal of discussion, some of it, I fear, based on an incomplete understanding of the matter. I refer to the problem of payment of special account benefit in cases where hospitals are not "recognized" for the purpose of the special account plan.

Last year the Government introduced legislation under which it became possible for the first time to pay hospital and medical fund benefit in cases of persons suffering from chronic or preexisting ailments, and in cases of long-term illnesses where it was necessary for a patient to remain in hospital longer than the period during which the Funds pay benefits under their rules. This removal of restrictions on payment of Fund benefit was a tremendous step forward in the Hospital Benefits Scheme, and its introduction has brought relief to a large number of persons most in need of help.

As I explained when I introduced the legislation last year, it would not be reasonable if this special account fund benefit plan was extended generally to patients in convalescent homes, benevolent homes, rest homes or homes for aged persons. Although these institutions are, in some cases, classified as private hospitals for the purposes of various State laws, they do not generally provide hospital treatment at a standard equivalent to that which is given at general public hospitals. The institutions concerned are not so much "hospitals" as the homes of the persons who are accommodated there. Generally, they are not nearly as costly to maintain as a normal hospital because they do not provide the full hospital treatment which a hospital patient requires and receives.

Notwithstanding the very limited way in which these homes can be regarded as hospitals, the Commonwealth has nevertheless always accepted their patients as hospital patients for the purposes of payment of Commonwealth hospital benefit, and accordingly the patients in these institutions who are insured with a registered hospital benefits organization have been, still are and will continue to be entitled to payment of Commonwealth hospital benefits amounting in all to £7 per week. Many of these patients are Social Service pensioners and are thus entitled both to pension payments amounting now to £4 15s. a week, as well as Commonwealth Benefit of £1 per day if insured, thus giving them altogether £11 15s. a week from the Commonwealth towards the cost of their accommodation in these institutions.

The difficulty that has arisen in this matter is to establish a proper line of demarcation between hospitals and institutions of the type I have described. Because of the need to supervise these institutions, State health legislation requires them to be registered, and varying classifications are applied from State to State. Even if these classifications were uniform, the fact of being required to register under State legislation does not mean that any one of these institutions is a hospital providing full hospital treatment. Therefore it is necessary for the Commonwealth to apply its own criteria in deciding which institutions do, in fact, provide facilities and treatment on a basis comparable with that provided in public hospitals. In the Act that was passed last year this difficulty of definition was dealt with by excluding from entitlement to special account benefits patients in the various types of institutions I have mentioned and also in "institutions that provide accommodation principally for permanent patients". This expression, whilst adequately defining the types of institution intended to be excluded, has been found to be too restrictive. The Government has accordingly decided to redefine this class of institution, and the new definition, which is included in this Bill, will not include the expression "an institution that provides accommodation principally for permanent patients". The new definition will exclude benevolent homes, convalescent homes, homes for aged persons and rest homes and other institutions of this nature.

The effect of the new definition will be that special account benefit will, after January 1 next, be payable to patients in institutions which conform more closely to the conception of true hospitals.

The new definition will in addition provide that individual patients in homes which are not eligible for recognition will be entitled to payment of special account fund benefit when they can establish, firstly, that they were suffering from an illness or injury requiring treatment of the kind provided in public hospitals; and secondly, that the treatment provided was of a standard substantially equivalent to that which they would have received in a recognized public hospital.

I have explained this proposal at some length in the hope that misunderstandings which have arisen in the past will not in future cloud or hamper any discussion which honourable members wish to conduct on this subject.

Pharmaceutical Benefits.

I come now, Mr. Speaker, to those sections of the Bill which deal with the proposed changes in Pharmaceutical Benefits, and are perhaps more controversial than those to which I have just referred. In fact, they are already giving rise to some controversy, a good deal of which may proceed from an inadequate understanding of the Government's proposals.

First of all may I say, Sir, that the National Health Service is not something which is static and fixed, and should not be so regarded. It must be capable of modification and improvement from time to time as circumstances demand, and opportunities and resources permit, but at the same time this must be done in a way which is financially responsible, and properly correlated with the rest of the great structure of social services which the Government has built up, and which depends, in turn, on the vast national expansion, development and prosperity which have followed in the wake of its economic policy and which, like the celebrated monument to Sir Christopher Wren, one only has to look around to see.

It is, however, imperative in the national interest that expenditure on social welfare shall be properly controlled in relation to national objectives and to total resources; otherwise the social services will become an incubus and not an instrument designed to make life better. It is essential to remember that in the end the taxpayer must bear their entire cost, and therefore no responsible government could permit expenditure in one aspect of these services to expand uncontrolled, and with no element of stability.

When the Pharmaceutical Benefits Scheme was first introduced, it was decided to supply certain very important drugs to the public without a direct charge. No one could have foreseen that drugs of this type, which then represented a small area of total prescribing, and were almost entirely specific in use, would, within a few years, have their numbers, uses and purposes enormously expanded by fresh discoveries which have, in effect, produced what can only be described as a therapeutic revolution in the treatment of disease. It became, on every count, impossible to restrict the number of "free" pharmaceutical benefits

to a small range of prescribing, and to retain as pharmaceutical benefits a relatively small number of drugs. Inevitably the number of both drugs and prescriptions, and indeed of indications for their use, has increased, and in recent years at an accelerated pace.

There have been inevitable concomitant increases in cost. In the early years the scheme was comparatively stable, but with the discovery and development of new drugs this has ceased to be the case. In the first full year of operation, 1951-1952, the cost was approximately £7,600,000 per annum. Although the number of included drugs was still relatively small, for the year ended June 30, 1955, it had increased to £10,700,000. In the next year it was £11,800,000, and in the following year it was £11,700,000. It will be seen that it was in a condition of comparative stability. However, it was after this that the list of drugs began to expand rapidly. In the year ended June 30, 1958, the cost reached £15,000,000, an increase of over £3,000,000 in one year. In the last financial year it was £21,000,000, and the projected cost for the next financial year is several millions higher still. It is obvious that at this rate, and still for a limited range of drugs, the cost of pharmaceutical benefits could soon exceed £30,000,000 a year, and would dominate the entire National Health Service, leaving correspondingly less room for manoeuvre for improvements and operations in any other direction. May I emphasize again that every penny of this cost must be borne by the taxpayer, and that responsibility in government demands some attempt at stabilization in such circumstances.

The Government has, therefore, decided to make two changes.

Up to the present there have been two separate Pharmaceutical Benefit Schemes—a Pensioner Scheme and a General Scheme. Under the Pensioner Scheme, the Government has provided, free of charge to the patient, a full range of drugs and medicines for Social Service Pensioners who have been issued with a Pensioner Medical Service Entitlement Card. So far as this Scheme is concerned no change is proposed. Pensioners and their dependants, who are enrolled in the Pensioner Medical Service, will still continue to be eligible for a full range of drugs and medicines free of any charge.

Under the General Scheme, the position has been that there has been a limited list of drugs which the public generally has been entitled to receive free of charge. When medicines or drugs not included in this list have been prescribed by doctors, they have been supplied by chemists at the expense of the patient concerned—this expense varying from a few shillings in the case of the cheaper drugs to considerable amounts in the case of more expensive drugs. What the Government now proposes is firstly, that this General list will be very substantially widened so that it will cover practically the same comprehensive range as the Pensioner list, and secondly, that a charge of 5s. will be made to persons (other than pensioners) for drugs prescribed by doctors from this General list.

Considerable advantages will flow from this arrangement. For instance, instead of his present uncertainty, and sometimes anxiety, as to what it will cost him to obtain a drug or medicine prescribed for him by his doctor, every patient will now know what the cost will be. It will be 5s. or, in the case of cheaper drugs, the price the chemist charges.

I, of course, do not want to be understood to be promising that every prescription written for every patient will come within this new arrangement. In any scheme conducted by any government there would necessarily have to be some limitation of the range of drugs falling within it. I can, however, say that this new arrangement will apply to a very great majority of the drugs prescribed in the ordinary course of their work by doctors for patients. Broadly speaking, the range of drugs will be the same as that covered in the British Pharmacopoeia—the generally accepted official publication—with such additions as are recommended by the expert committee of doctors and chemists which is known as the Pharmaceutical Benefits Advisory Committee. There will be some exceptions, but for the most part these will be in relation to drugs which, in the opinion of this expert committee, are not appropriate for use other than for the treatment of a restricted list of diseases.

There are three groups of people who will be affected by the changes, and those interests must be properly considered. I shall discuss each in turn, though the order in which I do so does not mean that I assign more importance to one than the other.

First, the doctors—it is from this very wide range of drugs and medicines to which I have just referred that

doctors will have a choice of what to prescribe for their patients, and within it a doctor will not be hampered in his medical discretion by any consideration of the cost of the prescription to the patient. He will know that the patient will have to pay no more than 5s to the chemist for it. He will further know that there is no drug at all which the patient, unless he is a pensioner, can receive from the chemist free of cost altogether. In my view, this will greatly widen the doctor's freedom of choice as to the best drug to prescribe for his patient, and should remove some of the pressures to which he is at present subjected. I want to say that it is not to the discredit of anyone, but an inevitable effect of the development of the present system along the lines which I have described which has led to these pressures, and to a considerable prescribing of expensive drugs without regard to their cost to the Government, or, in other words, to the taxpayer. The Government believes that this widening of the area of choice for the doctor will be an advantage for him.

The second group is the pharmaceutical chemists, and this includes the Friendly Society dispensaries. The private chemists have made representations to me, through the Pharmaceutical Guild, about certain apprehensions which they entertain. These are, firstly, that they may be subjected to what may be described as unfair competition from the Friendly Society dispensaries, which, as honourable gentlemen will be aware, conduct their business on different lines to the private chemist, and secondly, they are concerned about the price to be paid by the Government for dispensing pharmaceutical benefits. These are proper subjects to be raised, and there can be no objection to their discussion. Everyone, Mr. Speaker, will want to see that they are settled on a basis of equity, and I believe that this is the view of both the private chemists and the Friendly Societies. I have, in fact, been engaged in discussions with both.

The Bill accordingly contains provisions which authorize chemists to charge 5s. on each prescription and provides that it will be a condition of a chemist's approval under the Act that he follow a practice of doing so for prescriptions, except of course those written for pensioners with Pension Medical Service Entitlement Cards. As a breach of a condition of approval makes a chemist liable to have his approval terminated, the legislation gives full effect to the Pharmaceutical Guild's expressed request that the charging of the fee should be mandatory on chemists.

The Bill provides also that Friendly Society dispensaries, like any other chemists, will follow the practice of charging the 5s. when supplying benefits to the public. Fees for prescriptions made up for the dispensaries' own members will be included in the capitation fees paid by the members of the Friendly Society's dispensary fund. The Government offers no objection to this method of charging the fees, and the Bill accordingly authorizes dispensaries to follow this practice.

It will, however, be necessary for the dispensaries to identify the member of the public from the member of the Friendly Society, and to treat him accordingly. Not only will strict administrative arrangements be enforced by the Government to ensure that this is done, but it will obviously be an interest of the Friendly Societies to do so; otherwise in a short time they will forgo the collection of what will amount to very large sums of money.

The pricing arrangements are also under discussion between the Government and the chemists. The passage of the Bill will not affect the continuation of these discussions, and all I need to say about them, Mr. Speaker, is that they can, I am sure, be brought to a conclusion on terms which, as I have said before in the House, will be fair not only to the pharmacist, but to the taxpayer, and these arrangements will be identical both for Friendly Societies and private chemists.

The third group is the public. May I repeat what I have said before, that under any system the taxpayer, in the end, pays the entire cost. It is not in the interests of the public that a scheme of social benefit should be unstable and uncontrolled in the amount it costs. The direct participation of the recipient in the cost of such schemes will introduce an element of control and stability, otherwise extremely difficult to obtain. This is a major interest of the public and is therefore part of this arrangement. It is important that social welfare schemes should be the responsibility of all, including the beneficiaries, unless they are indigent. It is also important that the burden of the recipient should not be too onerous. Arrangements will therefore be made to see that this is so. The Government believes that these proposals will introduce an element of stability and financial responsibility into the

provision of pharmaceutical benefits, which is at present lacking.

The Government does not, of course, claim, nor does anyone imagine, that there will be no further rise in the cost of pharmaceutical benefits. What it does claim, and on substantial grounds, is that these arrangements will be a major and effective step in reconciling the provision of social benefit with responsibility in public finance and with a maximum of professional freedom. We live in a changing world, and it is idle to imagine that the conditions of the past, or indeed those of the present, can be carried forward unchanged into the circumstances of the future. We must shape our policies and adapt our measures to fit changing conditions. Instruments of social welfare must be the servants and not the masters of those who use them. The doctrinaire mind and the political label are likely to be insufficient guides to action, and resiliency and adaptability become correspondingly important.

I believe, Mr. Speaker, that these measures are a very considerable improvement to the present National Health Service, and I therefore commend the Bill to the House.

these irresponsibles, who are destroying the goodwill built up over the years by the older detailers, who, incidentally, are all members of the Medical Representatives' Organization of Australia.

The executive of this organization expresses its regrets to Dr. Molesworth and his partner, and to those other gentlemen who have suffered inconvenience at the hands of the "irresponsible" acting as a medical representative. We have found that those who have become members of the Medical Representatives' Organization and availed themselves of the lectures which we conduct are striving to give service to the medical profession and are anxious to help rather than hinder.

Yours, etc.,

W. JOHN ARPS,
President.

Medical Representatives' Organization of Australia,

"The Albany",
201 Macquarie Street,
Sydney.

October 23, 1959.

Dut of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

THE INSPECTOR OF ANATOMY.¹

[From the *Australasian Medical Gazette*, August, 1884.]

IN abolishing the office of Inspector of Anatomy, we think an error has been committed by the Government of New South Wales. We do not for a moment expect that the Dean of the Faculty of Medicine and his subordinate staff at the Sydney University will be in any way less careful in exactly obeying the provisions of the Anatomy Act, or that they will be negligent of the necessary decencies in the treatment of bodies handed over to them for dissection at the Medical School in consequence: yet we think it advisable that out of that consideration which is always necessary to show to popular prejudices, especially as regards the treatment of the dead, that these facts should be certified to by some person in authority unconnected with the corporation interested. We cannot but regret that Dr. Belgrave, the late inspector, showed so little tact and judgement in his conduct of the duties of the office, and that its abolition was the consequence.

Correspondence.

DRUG HOUSE REPRESENTATIVES.

SIR: In his usual courteous manner, Dr. Molesworth has given me the opportunity to see his letter² before it was published, for which I am extremely grateful.

The problems raised by Dr. Molesworth are of recent origin in this profession, and are, I feel sure, the result of a number of "irresponsibles" being admitted to the ranks of medical representatives. The very wording of "Advertisements for Staff" opens the way for immaturity, as the general requirements are for men under the age of 30 years (preferably nearer 20 years), who have little if any appreciation of the ethics of medicine or, in fact, of ethics.

The substance of these complaints was ventilated at the September meeting of the Medical Representatives' Organization, and as far as our investigations can ascertain, not one member of the Medical Representatives' Organization has been involved in this mass exhibition of bad manners. Our organization is not a disciplinary body, neither do we interfere in the policy of any company, so it is the responsibility of the ethical companies to discipline their representatives and, if necessary, weed out

NEW AIDS TO RESPIRATION.

SIR: In "Current Comment", October 3, mention is made of various types of respirator aid for patients with respiratory paralysis. However, no mention is made of some of the problems associated with these procedures or of other alternatives.

The most notable omission is of glosso-pharyngeal breathing (G.P.B.). This technique has the great advantage of not requiring any outside power source. Its main disadvantage is that, although it becomes an automatic activity, it does not become so subconscious as to continue during sleep. However, cuirass type respirators are available for this purpose.

G.P.B. vital capacity can be as high as the anticipated normal figure, and a minute alveolar ventilation of 9 litres is usual with training. When this level is achieved, speech (including a call for help) and meals do not present any problem. Surely this is the most satisfactory independence for those patients whose vital capacity is reduced below 1000 ml. There is no lower limit of vital capacity for this technique to be effective. (Failures of G.P.B. due to weakness of bulbar muscle groups must be dependent on other less satisfactory alternatives mentioned in "Current Comment".) However, most failures are due to poor teaching techniques and inadequate attention to detail.

The use of a vacuum-cleaner motor for resuscitation has some real advantages. The room air is not as dry as cylinder gas, and air is far preferable to oxygen, which is often used for resuscitation. However, vacuum motors tend to overheat the outgoing air on hot days, and mechanical ruggedness has left a lot to be desired in prolonged use. Further, the high-pitched noise can be irritating and difficult to suppress.

Whereas the chest respirator works by causing descent of the diaphragm, the abdominal bag works by causing its ascent. Maximum efficiency of the former occurs at a body tilt such that the diaphragm has just commenced to float in equilibrium between intrapleural pressure and the hydrostatic intraabdominal pressure. In the obese this may not occur until the patient is tipped up to 30°; others may be best in a slightly head-down position. This position can alter in a particular patient, with transient changes in abdominal distension. In the abdominal bag type the foot-down tilt must be such that the diaphragm descends by at least 50% more than the required tidal volume and this again will depend on the degree of abdominal filling.

However, the pressure change at the diaphragm is a function of the sine of the angle of tilt of the trunk from horizontal, and 50% of this change will occur at 30° of foot-down tilt, and further tilting past 75° will give little useful additional volume change. Thus in the obese patient this type of respirator will be unable to produce a satisfactory volume exchange. In patients with a scaphoid abdomen, the closed-circuit nature of the bag-type respirator is mechanically attractive, since it requires a smaller motor unit than a cuirass and has a much greater mechanical efficiency.

In the first few months after onset, paradoxical respiration may reduce the efficiency to an unusable level in any respirator which depends for its function solely on diaphragmatic shift—i.e., rocking bed, cuirass or abdominal bag. At a later date chest-wall stiffness allows efficient

¹ From the original in the Mitchell Library, Sydney.

² MED. J. AUST., 1959, 2: 658 (October 31).

mechanical use of the diaphragm as a piston. In the absence of muscle recovery, attempts to maintain chest-wall mobility retard progress and are ill-advised.

None of the alternatives to the tank or box respirator, except the mouth pressure tube, are capable of high levels of ventilation, and will only work if the patient's ventilation has been adjusted to basal requirements controlled either by use of the Radford Nomogram or less satisfactorily by CO_2 tension determination.

We have four patients trained in G.P.B. and fitted with cuirass respirators living in their own homes; their vital capacities are 200, 300, 500 and 600, and their distances from Fairfield Hospital are 300, 10, 160 and 50 miles respectively. The two latter patients have only accessory muscle action and little (less than 200 ml.) of intercostal and diaphragmatic movement.

Yours, etc.,

PETER L. COLVILLE,

Poliomyelitis Division,
State Health Department.

19 Park Street,
South Yarra,
Melbourne.
October 13, 1959.

References.

BURKE, B. E. (1957), "Glossopharyngeal Breathing and its Use in the Treatment of Respiratory Poliomyelitis Patients, with Some Notes on Chest Respirators", *Aust. J. Physiother.*, 3: 5.

COLVILLE, P., SHUGG, C., and FERRIS, JR., B. G. (1956), "Effects of Body Tilting on Respiratory Mechanics", *J. appl. Physiol.*, 9: 19.

THE CASE AGAINST TONSILLECTOMY.

SIR: Dr. A. B. K. Watkins's letter is a fair comment. Equally, his simile about looking both ways before crossing the road would not be questioned in these days of road accidents.

Bar advocating care, he advances no other positive evidence. Nor even does he mention his indications for the benefit of all. I find these disputed even in the highest oto-laryngological circles. If so many patients are "denied" as he says, how is it still the commonest operation? Surely this would presuppose an enormous need. Amongst the "modern tendencies" that he decries is the advice now current in the United Kingdom for prophylactic poliomyelitis inoculation before operation.

However, I agree, no operation will live or die on its mortality statistics. It will depend on the benefits. It is these that I find difficult either to assess or to understand.

Yours, etc.,

Warrnambool Base Hospital,
Warrnambool,
Victoria.
October 13, 1959.

F. R. BRAITHWAITE.

SIR: That even the best do not know which cases require tonsillectomy is illustrated by the following observations.

1. About 40 children attend a teaching ear, nose and throat clinic at a big London hospital one afternoon. They have been referred by family doctors. A specialist takes a history, performs his examination, and says to Mum: "I think the tonsils and adenoids should be removed, however there is a two years' waiting list at this hospital." He writes to the family doctor, advising him to send the child back in 23 months so that the operation can be arranged then. Comment: If the operation is necessary, can it wait two years?

At the same clinic on the same afternoon, some children are reexamined who have already been seen 23 months before. In some cases the specialist says to Mum: "The child is better now and does not need the operation." Comment: Had there been no waiting list, it is to be presumed that an unnecessary operation would have been performed 23 months before.

2. A leading article in *The General Practitioner of Australia and New Zealand* of January 15, 1959, quotes an article which is stated to appear in the *Journal of Pediatrics*, Volume 52, 1958, at page 339. A Dr. Bakwin examined 1000 New York City schoolchildren; 610 had

already lost their tonsils. The remaining 390 were examined by a group of school physicians, who selected 45% for the operation and rejected the rest. The rejected children were examined by another group of physicians. They recommended 46% for operation. After three examinations, only 65 children of the original 1000 remained intact or unselected for this butchery.

3. Tonsils and adenoids often grow again after operation. We all see patients with tonsillitis who have been under the knife several times before, yet still present with the disease.

It is to be concluded from these observations that the indications for the operation are hazy.

The operation carries a mortality estimated to be one in 6000 in the United Kingdom (Registrar-General, 1950-1955). It cannot be denied that children die of hemorrhage in Australia too. How, then, can the conscientious general practitioner undertake the procedure?

In spite of the wonderful, brilliant, daring and often safe advances in modern medicine and surgery, it might be well for us all to recall the famous words of Ambroise Paré some centuries ago: "I dressed the man, God healed him" (rough translation). Perhaps many of us would prefer the word "Nature" to God. Undeniably the vast majority of children with recurrent tonsillitis recover in the end without sequel.

Yours, etc.,

S. K. ROGERS.

P.O. Box 460,
Mount Isa,
Queensland.
October 19, 1959.

EVALUATION OF THE HEALTH OF INFANTS FED FULL-STRENGTH COW'S MILK.

SIR: The data presented by Dr. MacMahon, Dr. Woodhill and Dr. Gibson (October 10, 1959) belie the conclusion that there was no reason to change the feeding of full-strength cow's milk to infants up to five months of age.

Twenty-two of the small series of 62 infants developed gastro-intestinal symptoms. If in only half of these cases the symptoms were attributable directly to the type of feeding used, then this régime would be inefficient despite its simplicity. Any discomfort in the infant, no matter how trivial it appears to the medical attendant, can cause a great deal of anxiety in the parent and, as a result, mar the ideal parent-infant relationship. This fact is well illustrated by the number of parents seeking "outside" advice for apparently unimportant symptoms in their babies. Most mothers would be prepared to master a slightly more complicated feeding formula if discomfort in their babies could be avoided.

Whilst being in full agreement concerning the inadvisability of changing the type of feeding without adequate reason, I feel the authors have failed to appreciate the distress that "hard pellet-like stools" can cause in an infant. The "critical evaluation" of the high incidence of constipation in this series, and the indictment of the hot summer as the cause of this, is noticeably lacking a control. Unless it can be shown that constipation is just as frequent in infants fed on a lower protein diet, then here is a point against general acceptance of this routine.

I would draw the attention of the authors to the Borden Award Address delivered by Professor May¹ to the American Academy of Pediatrics. Here it is stated:

If under the guise of simplicity and generosity, the use of unmodified whole cow's milk should gain adherents, the unsuspecting infants will receive 22% of their calorie intake as protein! . . . To justify intakes of protein greatly in excess of that received by infants fed at the breast . . . the onus of proof has shifted onto the advocates of high intake of protein; and the mere survival of hosts of infants over the years, unwarranted extrapolations from remotely relevant and limited studies of lower animals and poorly designed and uncontrolled studies with infants must not be accepted as substantial arguments.

Yours, etc.,

ROBERT MORRIS.

130 Glebe Road,
Mereether,
Newcastle, N.S.W.
October 13, 1959.

¹ *Pediatrics*, 1959, 2: 384.

Australasian Medical Publishing Company Limited.

ANNUAL MEETING.

THE adjourned annual meeting of the Australasian Medical Publishing Company Limited was held at The Printing House, Seamer Street, Glebe, N.S.W., on October 21, 1959, Dr. W. L. Calow, the Vice-Chairman, in the chair.

Directors' Report.

The report of the Directors of the Company was as follows:

The Directors submit their report for the twelve months ended June 30, 1959, together with the balance sheet as at June 30, 1959, and the profit and loss account for the twelve months ended June 30, 1959.

THE MEDICAL JOURNAL OF AUSTRALIA continues to gain in popularity, and there has been a further rise in circulation. During the year arrangements were made for the table of contents to appear on the front cover commencing with the issue of July 4, 1959. This, we feel, will be of great assistance to readers.

A satisfactory result was obtained from the year's production of the printing and publishing department, and arrangements have been made for the payment of debenture interest for the year ended June 30, 1959.

The company's reserves are used in the business, and we consider the state of the company's affairs is satisfactory.

We wish to preserve the personal interest in the company of members of the several Branches of the British Medical Association in Australia. Therefore, when debentures registered in the name of a deceased holder are surrendered for redemption, we prefer to locate a buyer for them in the State where the deceased resided. It is thought that it would help to preserve this interest if some of the younger members of the Branches would purchase a number of these debentures.

Dr. A. E. Lee and Dr. W. F. Simmons retire from office by rotation in accordance with the Articles of Association (Article 39). They are eligible, and present themselves for re-election.

H. S. NEWLAND, Chairman.

September 29, 1959.

Election of Directors.

Dr. A. E. Lee and Dr. W. F. Simmons were re-elected to the Board of Directors.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Post-Graduate Conference at Bega.

THE Post-Graduate Committee in Medicine in the University of Sydney, in conjunction with the Far South Coast and Tablelands Medical Association, will hold a post-graduate conference in the Country Women's Association Rooms, Bega, on Saturday and Sunday, November 14 and 15, 1959. The programme is as follows:

November 14: 2 p.m., registration; 2.15 p.m., ophthalmic subject, Dr. Conrad Blakemore; 3.30 p.m., (a) "The Woman with a Stiff Tongue", (b) "Forecast and Follow-Up", Dr. Charles McCarthy.

November 15: 9.30 a.m., "Ante-Partum and Post-Partum Haemorrhage", Dr. George Cummins; 10.30 a.m., ophthalmic subject, Dr. Conrad Blakemore; 11.45 a.m., (a) "Do You Believe in A.D.?", (b) "A Book Bound in Black (Survey of Tranquillizing Drugs)", Dr. Charles McCarthy; 2.30 p.m., "The Use of Hormones in Gynaecology", Dr. George Cummins; 4 p.m., general meeting of the Far South Coast and Tablelands Medical Association.

An exhibition has been arranged by the New South Wales State Cancer Council during this week-end conference.

The fee for attendance is £3 3s., and those wishing to attend are requested to notify Dr. Reuben D. Glass, Honorary Secretary, Far South Coast and Tablelands Medical Association, Cobargo 7C, N.S.W. Telephone: Cobargo 120.

ROYAL PRINCE ALFRED HOSPITAL: EAR, NOSE AND THROAT DEPARTMENT.

Seminar Programme, 1959.

The staff of the ear, nose and throat department of the Royal Prince Alfred Hospital will conduct a seminar on the second Saturday of every month at 8 a.m. in the Scot Skirving Lecture Theatre. The main speaker will not exceed forty minutes, and there will be a discussion at the conclusion of his remarks. All medical practitioners and clinical students are invited to attend.

At the next seminar, to be held on November 14, 1959, Dr. B. B. Sheaves will speak on "Tracheostomy".

Notes and News.

A Meeting on the Relief of Pain in Childbirth.

A combined meeting, arranged by the New South Wales State Committee of the Royal College of Obstetricians and Gynaecologists and the Faculty of Anaesthetists of the Royal Australasian College of Surgeons, will be held on Friday, December 4, 1959, at 8.15 p.m., at the Stawell Hall, 145 Macquarie Street, Sydney. The subject of the meeting will be "Relief of Pain in Childbirth", and the speakers will be Dr. Kevin McCaul (Royal Women's Hospital, Melbourne), Dr. R. D. Macbeth (Women's Hospital, Crown Street, Sydney) and Dr. G. E. Cummins (King George V Hospital, Sydney). All medical practitioners are invited to be present.

The Australian Association of Physical Medicine and Rehabilitation.

The fourteenth annual meeting of the Australian Association of Physical Medicine and Rehabilitation was held on October 17, 1959, at Melbourne. The following office bearers were elected: President, Dr. R. Robinson (New South Wales); Senior Vice-President and President-Elect, Dr. A. Burnell (South Australia); Vice-President, Dr. G. Rich (New Zealand); Honorary Secretary and Treasurer, Dr. L. Wedlick (Victoria); Fifth Committee Member, Dr. N. Wing (New South Wales).

A scientific session followed the annual meeting, and the following papers were presented: "Rehabilitation Centre Report", Dr. N. Wing; "Results of Ultra-Sonic Therapy", Dr. J. Shanasy (read on his behalf by Dr. D. Meyers); "Management of the Amputee", Dr. R. Klein.

Fulbright Travel Grants, 1960-1961.

The United States Educational Foundation in Australia announces that, under the provisions of the *Fulbright Act*, travel grants are available to Australian citizens to go to the United States for study, research or lecturing at American universities and other institutions of higher learning during 1960-1961.

All candidates must fulfil the following requirements: (a) Candidates must hold a university degree or recognized professional qualifications. (b) Candidates must possess a guarantee of financial support in dollars for the proposed period of the visit to the United States. (c) Candidates must be affiliated with an approved American institution of higher learning. (d) The minimum period of study in the United States for students is one academic year. Lecturers must spend a minimum of one semester and research scholars three months in the United States (exclusive of travel time), of which about two-thirds should be spent at one university or recognized research institution. Grants cannot be given for attendance at conferences alone. (e) Candidates must be Australian citizens.

These travel grants are available for travel to the United States for or during the American academic year 1960-1961. All travel grants cover the cost of direct travel between the candidate's home in Australia and the institution he wishes to attend in the United States. No allowances are made for dependants' travel. All awards are made in open competition.

Applications are accepted in the following categories: (a) Visiting lecturers and research scholars (usually scholars at the post-doctoral level). The closing date for the receipt of applications is January 31, 1960. (b) Post-graduate students. The closing date for the receipt of applications is February 28, 1960. (c) Special categories awards (for

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persons whose professions do not require highly specialized academic qualifications). These are open to visiting lecturers, research scholars and students. The closing date is March 31, 1960. No applications can be accepted after the closing dates.

Further information and application forms may be obtained from the United States Educational Foundation, Box 89, G.P.O., Canberra, A.C.T.

Rockefeller Foundation Grants.

In the list of Rockefeller Foundation Grants for the second quarter of 1959, the following are noted with pleasure.

Dr. A. L. Williams, pathologist, Royal Children's Hospital, Melbourne, has received a grant of \$425 "to visit pediatric centers while in the United States".

The University of Adelaide has received a grant of \$10,000 for research on kuru, "a neurological disease occurring in New Guinea". The work is to be carried out under the direction of Professor H. N. Robson and Professor J. H. Bennett.

Dr. G. J. V. Nossal, of the Walter and Eliza Hall Institute of Medical Research, Melbourne, has been given a grant of \$2900 "to accept a fellowship at Stanford University, California".

Perth Chest Hospital Opened to Non-Tuberculous Patients.

The Commonwealth Minister for Health, Dr. D. A. Cameron, announced on September 30, 1959, that, because of the effectiveness of the control over tuberculosis in Western Australia, it had been found that some beds in Perth Chest Hospital were no longer required for the diagnosis or treatment of sufferers from that disease. He had accordingly given his approval for the admission of a number of non-tuberculous patients to this hospital, which had been provided at the expense of the Commonwealth Government in accordance with the joint Commonwealth and State agreement which aimed at the eventual eradication of the disease. The fact that the beds would not always be required for tuberculous patients had been taken into account during the planning and siting of new

chest hospitals in the various States. If the demand for beds for tuberculous patients continued to recede, still further beds at the Perth Chest Hospital would be released. Dr. Cameron said that the State Minister for Health, the Hon. Ross Hutchinson, M.L.A., and the officers of his Department were to be warmly congratulated on the high standards attained in Western Australia in the control of this formidable infectious disease.

Naval, Military and Air Force.

APPOINTMENTS.

The following appointments, changes etc. are published in the *Commonwealth of Australia Gazette*, No. 52, of August 27, 1959.

AUSTRALIAN MILITARY FORCES.

Citizen Military Forces.

Eastern Command.

Royal Australian Army Medical Corps (Medical).—2/191322 Captain D. M. Storey is appointed from the Reserve of Officers, 10th July, 1959. 2/165473 Major J. E. D. Goldie is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (Eastern Command), 9th December, 1958. 2/67299 Captain (provisionally) P. A. Stanton-Cook relinquishes the provisional rank of Captain, 21st June, 1959, is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical)) (Eastern Command) and is granted the honorary rank of Captain, 22nd June, 1959.

Southern Command.

Royal Australian Army Medical Corps (Medical).—3/97030 Major P. C. B. Bradley is appointed to command 4th Field Ambulance and to be temporary Lieutenant-Colonel, 1st July, 1959. 4/31963 Lieutenant-Colonel V. D. Plueckhahn relinquishes command 4th Field Ambulance, 30th June, 1959. 3/101028 Captain (provisionally) D. M.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED OCTOBER 3, 1959.¹

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	1	3(3)	1						5
Amoebiasis		..	3				3		6
Ancylostomiasis									
Anthrax									
Bilharziasis									
Brucellosis									
Cholera									
Chorea (St. Vitus)									
Dengue									
Diarrhoea (Infantile)	2	9(8)	2(2)				3		16
Diphtheria		1(1)							9
Dysentery (Bacillary)		2(2)					4		10
Encephalitis									
Filariasis									
Homologous Serum Jaundice									
Hydatid									
Infective Hepatitis	64(17)	14(18)	18(2)	8(5)	8(3)		1	1	114
Lead Poisoning			1						1
Leprosy							2		2
Leptospirosis									1
Malaria		1							1
Meningoococcal Infection	1(1)	3(3)		1(1)				2	7
Opthalmia									
Ornithosis									
Paratyphoid									
Plague									
Poliomyelitis									
Puerperal Fever									
Rubella		14(12)			9(1)	1(1)			18
Salmonella Infection					1(1)	1(1)			2
Scarlet Fever	7(3)	6(6)	5(4)	1(1)		1			20
Smallpox									
Tetanus									
Trachoma						109			133
Trichinosis									
Tuberculosis	28(24)	15(10)	26(9)	10(9)	9(2)	3(1)			101
Typhoid Fever					1				1
Typhus (Flea-, Mite- and Tick-borne)									
Typhus (Louse-borne)									
Yellow Fever									

¹ Figures in parentheses are those for the metropolitan area.

O'Sullivan ceases to be seconded whilst in the United States of America, 6th July, 1959. 3/101028 Captain (provisionally) D. M. O'Sullivan relinquishes the provisional rank of Captain, 6th July, 1959, is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical) (Southern Command)) and is granted the honorary rank of Captain, 7th July, 1959.

Western Command.

Royal Australian Army Medical Corps (Medical).—To be Captains (provisionally), 16th July, 1959—5/706708 Graham Neil Cumpston and 5/26611 Philip Llewellyn Nash. To be Lieutenant-Colonel, 11th April, 1959—5/21578 Major (temporary Lieutenant-Colonel) C. Stuart, M.C.

Royal Australian Army Medical Corps (Medical).—6/15263 Captain (provisionally) D. E. Anderson ceases to be seconded whilst in the United Kingdom, 14th July, 1959. 6/15879 Major K. S. Millingen is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical) (Tasmania Command)), 18th June, 1959. 6/15263 Captain (provisionally) D. E. Anderson relinquishes the provisional rank of Captain, 14th July, 1959, and is transferred to the Reserve of Officers (Royal Australian Army Medical Corps (Medical) (Tasmania Command)), in the honorary rank of Captain, 15th July, 1959.

Special Notice.

UNIVERSITY OF SYDNEY SENATE ELECTIONS.

OWING to an unfortunate oversight the name of Dr. John G. Watson was omitted from the list published in last week's issue of the Journal of medical men offering as candidates for election to the Senate of the University of Sydney. We greatly regret this error and offer Dr. Watson our sincere apologies.

Some details of Dr. Watson's qualifications and career are as follows:

WATSON, JOHN GLENTON: B.A., M.B., B.S., B.Ec.; graduated in Economics (evening student) in 1941 and in Arts (evening student) in 1948 whilst a secondary school teacher; graduated in Medicine in 1955; awarded Robin May Memorial Prize in final year of medical course; war service from 1942 to 1947; General Medical Practitioner; Honorary Clinical Assistant in Medicine, Sydney Hospital, since 1958; Committee Member, Eastern Suburbs Local Association of B.M.A., Delegate to Annual Meeting of Delegates of Local Associations, 1959; Vice-President of Sydney University Union, 1947-1948, President, 1948-1949; Vice-President, Sydney University Medical Society, 1955; Fellow of Senate of University of Sydney as Representative of Undergraduates, 1949-1955.

Royal Australasian College of Surgeons.

ANNUAL SCIENTIFIC MEETING, NEW ZEALAND.

NEW ZEALAND Fellows of the Royal Australasian College of Surgeons will be holding an annual scientific meeting in Dunedin on March 31 and April 1, 1960. The theme of the clinical section of the meeting will be "Surgery of the Endocrine System". A cordial invitation to attend is extended to Fellows resident in Australia. All information can be obtained from the Honorary Secretary of the New Zealand Dominion Committee, Mr. C. T. Collins, 16 The Terrace, Wellington.

Nominations and Elections.

THE undermentioned has applied for election as a member of the South Australian Branch of the British Medical Association:

Hensley, Annie D., M.B., B.S. (Univ. Melbourne), M.D., 1923, (Univ. Melbourne).

The undermentioned has been elected as a member of the South Australian Branch of the British Medical Association: Tathan, Peter H., M.B., Ch.B., 1959 (Univ. Cambridge).

Deaths.

THE following deaths have been announced:

CUMMING.—Phyllis Ellen Cumming, on October 22, 1959, at Turramurra, New South Wales.

SHELLSHEAR.—Cyril Shellshear, on October 24, 1959, at Brisbane.

Diary for the Month.

NOVEMBER 10.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
 NOVEMBER 11.—Victorian Branch, B.M.A.: Branch Meeting.
 NOVEMBER 12.—New South Wales Branch, B.M.A.: Public Relations Committee.
 NOVEMBER 13.—Queensland Branch, B.M.A.: Council Meeting.
 NOVEMBER 13.—Tasmanian Branch, B.M.A.: Branch Council.
 NOVEMBER 16.—Victorian Branch, B.M.A.: Finance Subcommittee.
 NOVEMBER 17.—New South Wales Branch, B.M.A.: Medical Politics Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference to an article in a journal the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of article. In a reference to a book the following information should be given: surname of author, initials of author, year of publication, full title of book, publisher, place of publication, page number (where relevant). The abbreviations used for the titles of journals are those of the list known as "World Medical Periodicals" (published by the World Medical Association). If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary is stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2-3.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this Journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in Australia can become subscribers to the Journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rate is £6 per annum within Australia and the British Commonwealth of Nations, and £7 10s. per annum within America and foreign countries, payable in advance.